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FILE 'HOME' ENTERED AT 10:34:18 ON 29 DEC 2001

=> fil capl

=> s amidon, g?/au
L1          299 AMIDON, G?/AU

=> s gelatin
          59755 GELATIN
          17588 GELATINS
L2        64592 GELATIN
                (GELATIN OR GELATINS)

=> s oral?
L3       194969 ORAL?

=> s l1 and (l2  (s) l3)
            630 L2 (S) L3
L4            0 L1 AND (L2 (S) L3)

=> s l1 and l2 and l3
L5            5 L1 AND L2 AND L3

=> d ibib abs kwic tot

L5   ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2001 ACS
Full-text
ACCESSION NUMBER:         2001:564810  CAPLUS
DOCUMENT NUMBER:          135:127231
TITLE:                    Controlled-release pharmaceutical containing comprises
                          a covered container with an aperture and an aperture
                          cover
INVENTOR(S):              Crison, John R.; Amidon, Gordon L.
PATENT ASSIGNEE(S):       Port Systems LLC, USA
SOURCE:                   PCT Int. Appl., 43 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     WO 2001054665      A1   20010802       WO 2001-US2352   20010125
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
             ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                    US 2000-177822   P  20000125
AB   A device for controlled release of pharmaceutical agents and a method for
     use of the device.  The drug delivery device comprises a covered container
     with an aperture and an aperture cover, contg. a pharmaceutical agent and
     an excipient formulation.  Acetaminophen/Carbopol 971P were compressed
     into cylindrical tablets, each weighing 0.28 g, so that the tablets fit
     into the capsule base for sizes #2 and #0.  The capsules were coated with
     a soln. comprising cellulose acetate 9, triacetin 1.4, and acetone 100%.
     Dissoln. rate of the capsules were tested.
REFERENCE COUNT:          1
REFERENCE(S):             (1) Eckenhoff; US 5000957 A 1991 CAPLUS
IN   Crison, John R.; Amidon, Gordon L.
IT   Gelatins, biological studies
     Organic compounds, biological studies
     Organometallic compounds
     Polymers, biological studies
     Polysaccharides, biological studies
     Polyurethanes, biological studies
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (controlled-release pharmaceutical contg. comprises covered container
        with aperture and aperture cover)
IT   Drug delivery systems
```

(**oral**, controlled-release; controlled-release pharmaceutical contg. comprises covered container with aperture and aperture cover)

L5 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2001 ACS
Full-text

ACCESSION NUMBER: 1998:805719 CAPLUS
DOCUMENT NUMBER: 130:213544
TITLE: Lipid-filled hard **gelatin** capsules as novel drug delivery systems with application to nifedipine
AUTHOR(S): Crison, John R.; Lipka, Elke; Kim, Jae Seung; **Amidon, Gordon L.**
CORPORATE SOURCE: TSRL Inc., Ann Arbor, MI, 48108, USA
SOURCE: Bull. Tech. Gattefosse (1997), 90, 71-75
CODEN: BTGRDQ; ISSN: 0397-7617
PUBLISHER: Gattefosse s.a.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In recent years, microemulsions have been studied extensively as a potential strategy for **oral** drug delivery. Microemulsions are particularly useful for improving the **oral** absorption of water insol. drugs by utilizing SMEDDS technol. (self-microemulsifying drug delivery systems) to enhance the soly. of the drug in the upper intestine. In this study, a water insol. drug with a high octanol-water partition coeff. and low aq. soly. (aq. soly. at 37° = 6 mg/mL) was formulated by using a semi-synthetic lipid/surfactant systems consisting primarily of satd. polyglycolyzed glycerides. The 2 self-emulsifying lipid systems developed differed only in the HLB (hydrophilic-lipophilic balance) of the cosurfactant; one formulation having a high HLB (14), the other having a low HLB (4). When placed in simulated gastric (pH 1.2) and intestinal (pH = 7.5) fluids at 37°, the formulations formed stable microemulsions with diams. in the 1 mm range. The relative bioavailability of these 2 formulations was detd. in dogs and compared to that of the bulk powder. The area under the plasma-time curve (AUC) for the lipid formulation with a high HLB cosurfactant was 5-fold greater than that of the powder and 2-fold greater than that of the lipid formulation with the low HLB. The results of these expts. suggest that the HLB values of the cosurfactant may play an important role in facilitating either the solubilization of the water insol. drug or permeation of the drug across the intestinal wall, or both. This work also illustrate the potential of using hard **gelatin** capsules for delivering lipid formulations of this type.

REFERENCE COUNT: 32
REFERENCE(S):
(2) Aboul-Enein, H; Analytical Properties of Drug Substances 1980, P87 CAPLUS
(3) Almgren, M; J Coll and Interface Sci 1981, V81, P486 CAPLUS
(4) Amidon, G; J Pharm Sci 1982, V71, P77 CAPLUS
(6) Brady, A; J Phys & Colloid Chem 1949, V53, P56 CAPLUS
(7) Braun, R; J Pharm Sci 1972, V61, P175 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Lipid-filled hard **gelatin** capsules as novel drug delivery systems with application to nifedipine
AU Crison, John R.; Lipka, Elke; Kim, Jae Seung; **Amidon, Gordon L.**
AB In recent years, microemulsions have been studied extensively as a potential strategy for **oral** drug delivery. Microemulsions are particularly useful for improving the **oral** absorption of water insol. drugs by utilizing SMEDDS technol. (self-microemulsifying drug delivery systems) to enhance the soly. of the drug in the upper intestine. In this study, a water insol. drug with a high octanol-water partition coeff. and low aq. soly. (aq. soly. at 37° = 6 mg/mL) was formulated by using a semi-synthetic lipid/surfactant systems consisting primarily of satd. polyglycolyzed glycerides. The 2 self-emulsifying lipid systems developed differed only in the HLB (hydrophilic-lipophilic balance) of the cosurfactant; one formulation having a high HLB (14), the other having a low HLB (4). When placed in simulated gastric (pH 1.2) and intestinal (pH = 7.5) fluids at 37°, the formulations formed stable microemulsions with diams. in the 1 mm range. The relative bioavailability of these 2 formulations was detd. in dogs and compared to that of the bulk powder. The area under the plasma-time curve (AUC) for the lipid formulation with a high HLB cosurfactant was 5-fold greater than that of the powder and 2-fold greater than that of the lipid formulation with the low HLB. The results of these expts. suggest that the HLB values of the cosurfactant may play an important role in facilitating either the solubilization of the water insol. drug or permeation of the drug across the intestinal wall, or both. This work also illustrate the potential of using hard

gelatin capsules for delivering lipid formulations of this type.
ST lipid **gelatin** capsule delivery nifedipine
IT Caprylic/capric triglycerides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ethoxylated; lipid-filled hard **gelatin** capsules as delivery systems with application to nifedipine)
IT Capsules (drug delivery systems)
Drug bioavailability
Hydrophile-lipophile balance value
Microemulsions (drug delivery systems)
Surfactants
(lipid-filled hard **gelatin** capsules as delivery systems with application to nifedipine)
IT Lipids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lipid-filled hard **gelatin** capsules as delivery systems with application to nifedipine)
IT 21829-25-4, Nifedipine
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(lipid-filled hard **gelatin** capsules as delivery systems with application to nifedipine)
IT 102-76-1, Triacetin 37321-62-3, Lauroglycol 121548-04-7, Gelucire44/14
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lipid-filled hard **gelatin** capsules as delivery systems with application to nifedipine)

L5 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2001 ACS
Full-text
ACCESSION NUMBER: 1996:522252 CAPLUS
DOCUMENT NUMBER: 125:230594
TITLE: Drug delivery utilizing a novel programmable **oral** release technology: in vivo - in vitro correlation of release times
AUTHOR(S): Lipka, E.; Kim, J.S.; Siersma, C.A.; Crison, J.R.; **Amidon, G.L.**
CORPORATE SOURCE: TSRL Inc., Ann Arbor, MI, 48108, USA
SOURCE: Proc. Int. Symp. Controlled Release Bioact. Mater. (1996), 23rd, 575-576
CODEN: PCRMEY; ISSN: 1022-0178
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A delivery system comprising a **gelatin** capsule coated with a semipermeable membrane, an osmotic charge mixed with the drug and an insol. plug reproducible deliverys drugs at predetd. time pts. The capsule demonstrated a strong correlation between its in vitro and in vivo release time. This new formulation allows timed drug delivery to defined parts of the gastrointestinal system as well as administration of one dosage form with multiple pulsatile doses, thus reducing the dose frequency.
TI Drug delivery utilizing a novel programmable **oral** release technology: in vivo - in vitro correlation of release times
AU Lipka, E.; Kim, J.S.; Siersma, C.A.; Crison, J.R.; **Amidon, G.L.**
AB A delivery system comprising a **gelatin** capsule coated with a semipermeable membrane, an osmotic charge mixed with the drug and an insol. plug reproducible deliverys drugs at predetd. time pts. The capsule demonstrated a strong correlation between its in vitro and in vivo release time. This new formulation allows timed drug delivery to defined parts of the gastrointestinal system as well as administration of one dosage form with multiple pulsatile doses, thus reducing the dose frequency.
ST drug delivery programmable **oral** release
IT Drug bioavailability
Solution rate
(drug delivery utilizing programmable **oral** release technol.)
IT Pharmaceutical dosage forms
(capsules, controlled-release, drug delivery utilizing programmable **oral** release technol.)
IT 103-90-2, Acetaminophen
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug delivery utilizing programmable **oral** release technol.)

L5 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2001 ACS
Full-text

ACCESSION NUMBER: 1996:521723 CAPLUS
DOCUMENT NUMBER: 125:230345
TITLE: A novel programmable **oral** release technology for delivering drugs: human feasibility testing using gamma scintigraphy
AUTHOR(S): Crison, J.R.; Siersma, P.R.; **Amidon, G.L.**
CORPORATE SOURCE: TSRL, Inc., Ann Arbor, MI, 48108, USA
SOURCE: Proc. Int. Symp. Controlled Release Bioact. Mater. (1996), 23rd, 51-52
CODEN: PCRMEY; ISSN: 1022-0178
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A novel programmable **oral** drug delivery system was developed capable of site-specific delivery of multiple doses/drugs administered in a single unit. This dosage form consists of a **gelatin** capsule, a semi-permeable membrane coating, an insol. plug, and an osmotic charge, each of which can be rate-limiting to the release of the contents. The release time for the active ingredient of this delivery system is a function of the permeability of the film coating surrounding the dosage form, the length of the plug and the osmotic strength of the formulation. The delivery system was formulated to release a single dose of labeled compd. at a predetd. time. The capsules were administered to 6 human subjects under fed and fasted conditions in a crossover design and followed through the gastrointestinal tract using gamma scintigraphy. The release of the labeled compd. from this delivery system was reproducible and was not greatly affected by the presence of food. In addn., the in vitro release was a reasonable predictor of the in vivo release.

TI A novel programmable **oral** release technology for delivering drugs: human feasibility testing using gamma scintigraphy

AU Crison, J.R.; Siersma, P.R.; **Amidon, G.L.**

AB A novel programmable **oral** drug delivery system was developed capable of site-specific delivery of multiple doses/drugs administered in a single unit. This dosage form consists of a **gelatin** capsule, a semi-permeable membrane coating, an insol. plug, and an osmotic charge, each of which can be rate-limiting to the release of the contents. The release time for the active ingredient of this delivery system is a function of the permeability of the film coating surrounding the dosage form, the length of the plug and the osmotic strength of the formulation. The delivery system was formulated to release a single dose of labeled compd. at a predetd. time. The capsules were administered to 6 human subjects under fed and fasted conditions in a crossover design and followed through the gastrointestinal tract using gamma scintigraphy. The release of the labeled compd. from this delivery system was reproducible and was not greatly affected by the presence of food. In addn., the in vitro release was a reasonable predictor of the in vivo release.

ST **oral** drug delivery capsule scintigraphy

IT Solution rate
(novel programmable **oral** release technol. for delivering drugs)

IT Pharmaceutical dosage forms
(capsules, novel programmable **oral** release technol. for delivering drugs)

IT 12651-43-3, Ytterbium oxide 13465-55-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(novel programmable **oral** release technol. for delivering drugs)

L5 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2001 ACS
Full-text
ACCESSION NUMBER: 1995:843436 CAPLUS
DOCUMENT NUMBER: 123:350030
TITLE: Programmable **oral** release technology, PORT Systems: A novel dosage form for time and site specific **oral** drug delivery
AUTHOR(S): Crison, J. R.; Siersma, P. R.; Taylor, M. D.; **Amidon, G. L.**
CORPORATE SOURCE: TSRL, Inc., Ann Arbor, MI, 48108, USA
SOURCE: Proc. Int. Symp. Controlled Release Bioact. Mater. (1995), 22nd, 278-9
CODEN: PCRMEY; ISSN: 1022-0178
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The length of time to release contents increased as the nol. of layers of film coatings increased on the dosage form (**gelatin** capsules). This is due to a corresponding increase in film thickness and decreased

permeability. The range of av. release times for this system were highly reproducible and ranged from 15 min to 9h. This delivery system will be useful for delivering drugs to optimal permeability targets in the GI tract, delivering multiple doses from a single dosage form and avoiding site specific degrdn.

TI Programmable **oral** release technology, PORT Systems: A novel dosage form for time and site specific **oral** drug delivery

AU Crison, J. R.; Siersma, P. R.; Taylor, M. D.; **Amidon, G. L.**

AB The length of time to release contents increased as the nol. of layers of film coatings increased on the dosage form (**gelatin** capsules). This is due to a corresponding increase in film thickness and decreased permeability. The range of av. release times for this system were highly reproducible and ranged from 15 min to 9h. This delivery system will be useful for delivering drugs to optimal permeability targets in the GI tract, delivering multiple doses from a single dosage form and avoiding site specific degrdn.

ST programmable **oral** drug release

IT Solution rate
(programmable **oral** release technol., PORT systems: a dosage form for time and site specific **oral** drug delivery)

IT Pharmaceutical dosage forms
(capsules, controlled-release, programmable **oral** release technol., PORT systems: a dosage form for time and site specific **oral** drug delivery)

IT Pharmaceutical dosage forms
(**oral**, controlled-release, programmable **oral** release technol., PORT systems: a dosage form for time and site specific **oral** drug delivery)

```
=> fil biosis

=> s amidon, g?/au
L6         337 AMIDON, G?/AU

=> s oral?
L7      259981 ORAL?

=> s gelatin
          9581 GELATIN
           142 GELATINS
L8        9649 GELATIN
                 (GELATIN OR GELATINS)

=> s l6 and l7 and l8
L9           0 L6 AND L7 AND L8

=> s l6 and l8
L10          0 L6 AND L8

=> s l6 and l7
L11        126 L6 AND L7

=> s l11 and gelatin
          9581 GELATIN
           142 GELATINS
          9649 GELATIN
                 (GELATIN OR GELATINS)
L12          0 L11 AND GELATIN

=> fil uspatfull

=> s amidon, g?/au
L13         16 AMIDON, G?/AU

=> s l13 and orl and gelatin
           200 ORL
             5 ORLS
           204 ORL
                 (ORL OR ORLS)
         77064 GELATIN
          3372 GELATINS
         77911 GELATIN
                 (GELATIN OR GELATINS)
L14          0 L13 AND ORL AND GELATIN
```

```
=> s l13 and oral and gelatin
         85273 ORAL
            15 ORALS
         85282 ORAL
                 (ORAL OR ORALS)
         77064 GELATIN
          3372 GELATINS
         77911 GELATIN
                 (GELATIN OR GELATINS)
L15         11 L13 AND ORAL AND GELATIN

=> s solub? and l15
        327777 SOLUB?
L16         11 SOLUB? AND L15

=> d ibib abs kwic tot

L16  ANSWER 1 OF 11  USPATFULL
Full-text
ACCESSION NUMBER:        2001:43749  USPATFULL
TITLE:                   Multi-stage drug delivery system
INVENTOR(S):             Crison, John R., Ann Arbor, MI, United States
                         Amidon, Gordon L., Ann Arbor, MI, United States
PATENT ASSIGNEE(S):      Port Systems, L.L.C., Ann Arbor, MI, United States
                         (U.S. corporation)

                              NUMBER       KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 6207191          B1   20010327
APPLICATION INFO.:       US 1999-372913           19990812  (9)
RELATED APPLN. INFO.:    Continuation of Ser. No. US 1997-946515, filed on 7 Oct
                         1997, now patented, Pat. No. US 5976571
                         Continuation-in-part of Ser. No. US 1995-383830, filed
                         on 6 Feb 1995, now patented, Pat. No. US 5674530,
                         issued on 7 Oct 1997 Division of Ser. No. US
                         1994-251731, filed on 31 May 1994, now patented, Pat.
                         No. US 5387421, issued on 7 Feb 1995 Continuation of
                         Ser. No. US 1992-826253, filed on 27 Jan 1992, now
                         abandoned Continuation of Ser. No. US 1991-648968,
                         filed on 31 Jan 1991, now abandoned
DOCUMENT TYPE:           Utility
FILE SEGMENT:            Granted
PRIMARY EXAMINER:        Bawa, Raj
LEGAL REPRESENTATIVE:    Hudak & Shunk Co. LPA
NUMBER OF CLAIMS:        20
EXEMPLARY CLAIM:         1
NUMBER OF DRAWINGS:      16 Drawing Figure(s); 7 Drawing Page(s)
LINE COUNT:              1013
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB      A drug delivery system (10) includes a first capsule half (12) having an
        inner chamber (16) containing a drug (18) therein. A plug (28) is
        disposed in a passageway (26) of the capsule half (12) for plugging the
        opening (24) thereof. The plug (28) is releasable from the passageway
        opening (24) upon the application of pressure from within the inner
        chamber (16). A pump mechanism, reactive with the external environment
        of the capsule half (12), causes an increase in pressure within the
        inner chamber (16) and forces the plug (28) out of the passageway (26)
        to release the drug (18) from the inner chamber (16) and out of the
        passageway (26). Thusly, after initial release of drug from a second
        capsule half (14) releasably mounted on the first capsule half (12), the
        first capsule half (12) provides a second pulse of drug release at a
        predetermined time after initial ingestion of the capsule. The invention
        further provides a method of manufacturing the drug delivery system (10)
        and method by which the drug delivery system (10) provides the drug to a
        body.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IN      Amidon, Gordon L., Ann Arbor, MI, United States
SUMM    It has been recognized that there is a need for a drug delivery system
        which yields an increase in the oral dosing interval of drugs
        exhibiting presystemic loss metabolism while simultaneously maintaining
        bioavailability equivalent to the immediate release dosage form. Such
        drugs would otherwise either require short interval dosing, such as
        periodic oral dosing having short periods between each oral dosing.
```

SUMM . . . for emitting external fluid into the osmotic device. The device includes an opening having an erodible element, such as a **gelatin** plug that erodes and forms an osmotic passageway in the environment of use. Within the device is a modulating agent in nonequilibrium proportions. Upon the influx of fluid into the device, there is co-**solubilization** of a useful agent which is then released from the device. Thusly, co-**solubilization** of a modulating agent and a useful agent controls the release of the useful agent and results in the delayed. . .

SUMM . . . of drug will escape metabolism and therefore be available. For those drugs with incomplete absorption due to low permeability, poor **solubility** or in which case the absorption rate limited by rate of dissolution, enhancers can be added to increase the bioavailability.. . .

DETD The capsule halves 12,14 can be made from various materials, preferably water containing **gelatins**.

DETD . . . checked from three spots in the mortar taking one gram sample. A 98.4% yield was obtained. A number zero hard **gelatin** two piece capsule was filled with 350 mg+/-1.5 mg of the fill mix or adjusted to give a potency of. . .

DETD . . . mg+/-1 mg of the captopril immediate release blend (50%) was disposed into the cap of the size number zero hard **gelatin** and mounted onto the capsule previously referred to above. The cap was placed on the body taking care not to. . .

DETD . . . coating or immersion coating of the capsules 12 include acetone for water insoluble materials and water (H O) for water **soluble** coating materials. Other suitable solvents known to those skilled in the art can also be used.

DETD A number zero hard **gelatin** two piece capsule (Capsugel, Greenwood, S. C.) was filled with 200 mg of the osmotic charge (sorbitol/lactose)-aspirin formulation. Gelucire 50/02. . .

DETD Capsules, prepared as described above numbered from 3 to 7, were used for bioavailability study. Captopril tablets and powder for **oral** and intravenous studies were kindly donated by Squibb. Two male beagle dogs, weighing thirty-four and thirty pounds and two midgut-fistulated. . .

DETD **Oral** study--Four tablets containing 25 mg of Captopril were given to four dogs orally with 20 ml of tap water. Dogs. . .

DETD The study was duplicated in each dog. The experimental design was the same as the **oral** study except that the schedule for sample collection was every one hour for twelve to thirteen hours. Dogs were released. . .

DETD . . . time zero to infinity by extrapolating the last blood concentration with an elimination rate constant (ke) were evaluated from the **oral**, intravenous, and technology studies based on the noncompartmental analysis. Relative bioavailability of technology capsules were determined comparing to the **oral** study and normalized by the dose given.

DETD Size 0, hard **gelatin** capsules were coated with cellulose acetate which was dissolved in acetone and ethanol. Triacetin was used as a plasticizer. The. . .

DETD Caps were removed from size 2 hard **gelatin** capsules (Capsugel®) and the bodies were manually dipped into a (9% w/v acetone +1.4% w/v triacetin) solution of cellulose acetate. . .

DETD Size 1 hard **gelatin** capsules (Capsugel®) were dipped into a solution of 15 gm polyurethane (Spenkel F78-M-50, Reichold) in 30 gm of acetone, USP/NF. . .

DETD . . . Cellulose, NF 97.35
Sorbitol, NF 35.00
Croscarmellose Sodium, NF 7.00
Magnesium Stearate, BP 1.75
Gelocire 50/02 120.00
Size #0 hard **gelatin** two piece capsules 66.00
Captopril immediate release blend (50%)
Coating solution for captopril pulsatile q.s. to obtain release capsules suitable. . .

L16 ANSWER 2 OF 11 USPATFULL
Full-text
ACCESSION NUMBER: 2000:160989 USPATFULL
TITLE: Enhancing the bioavailability of proteolytically labile therapeutic agents
INVENTOR(S): **Amidon, Gordon L.**, Ann Arbor, MI, United States
Leesman, Glen D., Hamilton, MT, United States
Sinko, Patrick J., Lebanon, NJ, United States
PATENT ASSIGNEE(S): Port Systems, LLC, Ann Arbor, MI, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6153592		20001128	
APPLICATION INFO.:	US 1994-244715		19940908	(8)
	WO 1992-US9336		19921109	
			19940908	PCT 371 date
			19940908	PCT 102(e) date

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Sayala, Chhaya D.
LEGAL REPRESENTATIVE: Gifford, Krass, Groh, Sprinkle, Anderson & Citkowski, P.C.
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
LINE COUNT: 833
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Proteins or peptidic substances, which may be prepared from naturally occurring proteins, enhance the bioavailability of proteolytically-labile therapeutic agents which, in the absence of the protein or peptidic substance would suffer enzymatic inactivation upon administration.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IN **Amidon, Gordon L.**, Ann Arbor, MI, United States

SUMM . . . in very low bioavailability because of hydrolysis of the peptides by proteolytic enzymes. For leuprolide, this ranges from 0.05% following **oral** administration to 38% following vaginal administration; for insulin, the corresponding figures are 0.05% and 18%. Lee, Journal of Controlled Release,. . .

SUMM Cho and Flynn; International Patent Application WO-90/03164 (1990) disclose the use of protease inhibitors in **oral** formulation but do not describe the nature of such inhibitors in detail; the only protease inhibitor which appears in the. . .

SUMM Kidron, et al; U.S. Pat. No. 4,579,730 (1986) disclose the use of protease inhibitors in **oral** formulation of insulin. Soybean flour is disclosed as a source of soybean trypsin inhibitor (Bowman-Birk trypsin/chymotrypsin inhibitor; molecular weight 8000. . .

SUMM Ziv, et al; Biochem. Pharmacol. 36, 1035-1039 (1987) disclose the use of the protease inhibitor aprotinin to enhance the **oral** absorption of proteins.

SUMM . . . East German Patent DD 252 539 A1 (1987) disclose the use of epsilon-aminocaproic acid and aprotinin as protease inhibitors in **oral** formulation of peptides.

SUMM Lee; J.; Controlled Release 13, 213-223 (1990) reviews the use of protease inhibitors in formulations of peptides for **oral**, nasal, buccal, rectal, vaginal, pulmonary, and ocular routes.

SUMM . . . with pepsin under temperature and pH conditions conducive to hydrolysis of protein. The glycinin is hydrolyzed with pepsin until its water-**solubility** is increased to 40-50%. Similarly, U.S. Pat. No. 2,502,482 by Sair et al. reports the enzymatic modification of glycinin with pepsin to produce an isolate wherein at least 60% by weight of the pepsin modified isolate is water-**soluble** at a pH 5.0.

SUMM . . . purified natural proteins, and filtered, solvent-extracted, molecular weight-fractionated or partially hydrolyzed proteins hereinafter referred to as protecting agents enhance the **oral**, nasal, rectal and vaginal bioavailability of proteolytically-labile therapeutic agents which, in the absence of the protecting agents, would suffer enzymatic inactivation upon attempted **oral**, nasal, rectal or vaginal administration.

SUMM . . . thereby enhance the bioavailability of pharmaceutical agents that are labile to certain proteases that can degrade the pharmaceutical agents upon **oral**, nasal, vaginal or rectal administration. Coadministration of these protecting agents with the labile pharmaceutical agents results in (1) competitive occupancy. . .

SUMM . . . depend upon the route of administration, the lability of the therapeutic agent, and the dose of the therapeutic agent. For **oral**, rectal, and vaginal administration, the protecting agent will generally be dosed at about 10-1500 mg. In the case of orally-dosed. . .

DETD Processing of Commercial Proteins and Flours. Fractionation by **Solubilization**. Soy Flour.

DETD . . . at room temperature. The mixture was allowed to settle, the supernatant drawn off, centrifuged, and filtered. In this way the directly-**soluble** fraction was obtained for recovery and use or further processing.

DETD Processing Of Commercial Proteins and Flours. Molecular Weight Fractionation by **Solubilization** and Dialysis. Soy Flour

DETD . . . solution of decanted and filtered soy flour which was processed further as follows to achieve molecular weight (MW) discrimination. The **solubilized** fraction was evaporated to dryness at 55° C. in a vacuum oven. The evaporate was dissolved in water and dialyzed. . . of 24 hours with periodic changes of dialysing medium. The retentates were evaporated giving 1.17 g of a >1000 MW **solubilized** soy flour fraction.

DETD Processing of Commercial Proteins and Flours. Molecular Weight Fractionation by **Solubilization** and Ultrafiltration (UF): 1K-30K and 30K-100K Fraction.

DETD Enhancement of Terlakiren **Oral** Absorption by Protecting Agents in Dogs

DETD Renin antagonist tripeptide terlakiren (200 mg of solid crystalline drug powder in a hard **gelatin** capsule formulation) was coadministered to four fasted Beagle dogs with an aqueous slurry of 1 g of the test inhibitor. . .

DETD . . . from Protein Technologies Inc.) and a 1 30K fraction of processed soy flour (prepared as in Example 3) enhance the **oral** bioavailability of terlakerin, a chymotrypsin-labile therapeutic agent.

DETD . . . inhibition was determined using filtered soy flour, 30K-100K fraction. This lot of processed soy flour was prepared according to the **solubilization** and ultrafiltration method described in Example 3. The results are given in Table IX and demonstrate that the tested processed. . .

L16 ANSWER 3 OF 11 USPATFULL

Full-text

ACCESSION NUMBER:	1999:155242 USPATFULL		
TITLE:	Method and formulation for increasing the bioavailability of poorly water-**soluble** drugs		
INVENTOR(S):	Crison, John R., Ann Arbor, MI, United States **Amidon, Gordon L.**, Ann Arbor, MI, United States		
PATENT ASSIGNEE(S):	Port Systems L.L.C., Ann Arbor, MI, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5993858		19991130
APPLICATION INFO.:	US 1997-867161		19970613 (8)
	NUMBER		DATE
PRIORITY INFORMATION:	US 1996-19797		19960614 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Page, Thurman K.		
ASSISTANT EXAMINER:	Spear, James M.		
LEGAL REPRESENTATIVE:	Kohn & Associates		
NUMBER OF CLAIMS:	12		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 4 Drawing Page(s)		
LINE COUNT:	510		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A self-microemulsifying excipient formulation for increasing the bioavailability of a drug which includes an emulsion including an oil or other lipid material, a surfactant, and a hydrophilic co-surfactant. A method for making a drug delivery system for increasing the bioavailability of a drug by emulsifying at least one drug with a self-microemulsifying excipient comprising an oil or other lipid material, a surfactant, and a hydrophilic co-surfactant and drugs formulated thereby.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Method and formulation for increasing the bioavailability of poorly water-**soluble** drugs

IN **Amidon, Gordon L.**, Ann Arbor, MI, United States

SUMM It is well known in the art that there are solid drugs which are scarcely **soluble** in water. Due to their low **solubilities**, these drugs have a correspondingly low degree of bioavailability.

SUMM Several prior art processes have been developed in efforts to increase the **solubility** and, hence, the bioavailability of poorly **soluble** pharmaceuticals or drugs. One such prior art process discloses the use of water-**soluble** high-molecular weight substances having low melting points, such as Carbowax, in combination with an insoluble drug.

However, compositions prepared by. . .

SUMM Other methods of increasing the aqueous dissolution rate of poorly water-**soluble** drugs include the use of organic solvents to **solubilize** the poorly water-**soluble** drug or pharmaceutical composition. One such method is disclosed in U.S. Pat. No. 4,540,602 to Motoyama et al., issued Sep.. . . 10, 1985, which discloses a process for the preparation of activated pharmaceutical compositions containing a solid drug that is scarcely **soluble** in water. The method includes the steps of dissolving or **solubilizing** a solid drug, that is highly insoluble in water, in a low-boiling point hydrophobic organic solvent such as lecithin. The **solubilized** drug is then emulsified in the presence of a water-**soluble**, high-molecular weight substance, such as **gelatin**, and the drug is removed from the emulsion.

SUMM The method disclosed in the Motoyama et al. reference **solubilizes** the drug and then resolidifies/recrystalizes the drug in a water-**soluble** matrix such as **gelatin** or lecithin. The Motoyama et al. method requires the use of organic solvents in order to **solubilize** the drug. This method has several inherent disadvantages or drawbacks. First, since the drug is **solubilized** and then recrystalized, the recrystalized product must be reidentified since polymorphic changes can occur when the drug is recrystalized in. . . Additionally, since the compounds of interest in the Motoyama patent are water-insoluble, organic solvents must be used in order to **solubilize** the drugs of interest. The use of organic solvents creates further problems with the health and safety aspects of organic. . . the use of organic solvents considerably add to the cost of utilizing organic solvents in a method to increase the **solubility** of water-insoluble drugs as organic solvent recovery and containment devices are very costly. Other known surface active excipients can be. . .

SUMM In recent years, microemulsions have been extensively studied as a potential modality for **oral** drug delivery. Microemulsions are particularly useful for improving the **oral** absorption of water insoluble drugs, such as proteins, by utilizing self-microemulsifying drug delivery systems (SMEDDS) to enhance the **solubility** of the drug in the upper intestine [Ritschel, 1980]. In particular, microemulsions have gained considerable notoriety as drug delivery systems. . .

SUMM The interest in the use of microemulsions as **oral** drug delivery systems stems from their ability to spontaneously form (emulsify) at a given temperature, their considerable **solublizing** properties, the ability to be sterilized by filtration, and high physical stability [Sarciaoux et al., 1995]. Another desirable feature of. . . form a microemulsion when exposed to gastrointestinal fluids. This type of behavior makes SMEDDS good candidates for vehicles for the **oral** delivery of lipophilic or slightly water-**soluble** drugs.

SUMM . . . surfactant, LAUROGLYCOL (propylene glycol laurate, HLB=4), and TRANSCUTOL (diethylene glycol monoethyl ether) as the co-surfactants, and indomethacin as the slightly water-**soluble** drug. Farah et al. [1993] found that the higher the HLB value of the surfactant and co-surfactant mixture, the higher. . .

SUMM . . . would be advantageous and desirable to have a method of increasing the dissolution and bioavailability of peptides, lipophilic and poorly water-**soluble** drugs which avoids the drawbacks of the prior art methods. Furthermore, it would be desirable to have a method which is completely aqueous-based in order to avoid the necessity for recharacterization of the pharmaceuticals or drugs according to the **solubilization** method disclosed above and also eliminating the cost and both health and environmental safety aspects of using organic solvents. It. . . gastro-intestinal administration. It would be a further advantage to have a self-microemulsifying excipient formulation in which the bioavailability of poorly water-**soluble** drugs can be increased by utilizing a co-surfactant having a high HLB which can be applied to a drug in. . .

SUMM By combining the method and self-microemulsifying formulation of the present invention with poorly water-**soluble** drugs or pharmaceutical compositions, optimal advantage can be taken of the potential potency and efficacy of poorly water-**soluble** drugs by increasing their bioavailability. The present invention provides an improved method and formulation for providing poorly water-**soluble** drugs with a means for a greater bioavailability which includes all of the aforementioned mentioned advantages.

DETD A self-microemulsifying excipient formulation for increasing the bioavailability of poorly water-**soluble** drugs or pharmaceutical compositions is disclosed. The formulation generally includes an emulsion including an oil or lipid material, a surfactant, and a hydrophilic co-surfactant. A poorly water-**soluble** drug or

pharmaceutical is emulsified in the self-microemulsifying excipient formulation thereby increasing the in vivo bioavailability of the drug or. . .

DETD . . . formulation at a time can be treated according to the present invention to yield a desired pharmaceutical composition. Additionally poorly water-**soluble** drugs and/or pharmaceutical ingredients can be treated according to the present invention and can then be used in combination with other drugs and/or pharmaceutical ingredients which may or may not be poorly water-**soluble**.

DETD . . . or other suitable solvents. Triacetin is suitable since it is miscible in the oil/lipid phase and can be used to **solubilize** a hydrophobic drug.

DETD . . . ingredient or formulation by emulsifying the drug with the self-microemulsifying excipient formulation of the present invention includes the steps of **solubilizing** a poorly water-**soluble** drug, pharmaceutical ingredient, or formulation thereof, in a mixture of surfactant, co-surfactant and solvent. The oil phase can then be suitably prepared, if necessary, by heating or other preparatory means and can then be added to the **solubilized** drug formulation and thoroughly mixed. The emulsion can then be added to a suitable dosage form such as soft or hard-filled **gelatin** capsules and allowed to cool.

DETD The relative proportions of surfactant and co-surfactant in the self-microemulsifying formulation of the present invention can influence the **solubilizing** and dissolution properties of the formulation. In general, the range of concentration of the surfactant/co-surfactant broadly ranges from 15 to. . .

DETD The lipophilic, poorly water-**soluble** active drug or pharmaceutical ingredient utilized in accordance with the present invention can include nifedipine, griseofulvin, cyclosporin, digoxin, itraconozole, carbamazepine,. . . indomethacin, steroids, ibuprofen, diazepam, finasteride, and diflunisal, for example. Other pharmaceutical ingredients or other drugs which are lipophilic or poorly water-**soluble** can also be used in accordance with the present invention. This list is not meant to be exhaustive, but rather. . .

DETD . . . present invention. Specifically, as described in greater detail below, applicant has demonstrated an improvement in the bioavailability of the poorly water-**soluble** drug, nifedipine, using a co-surfactant with a high HLB (HLB=14) value or that of a co-surfactant with a low HLB (HLB=4) value even though both formulations appeared to **solubilize** the drug equally. The area under the plasma-time curve (AUC) for the formulation with the high HLB co-surfactant was five. . . suggested that the HLB value of the co-surfactant plays an important role in increasing the bioavailability of lipophilic or poorly water-**soluble** drugs by possibly facilitating the **solubilization** of the poorly water-**soluble** drugs, by increasing the permeation of the drug across the intestinal wall, or both.

DETD . . . the fraction dose absorbed is inversely proportional to dose and is directly proportion to the dissolution rate. Therefore, in vivo **solubilization** and dissolution are important determinants of drug absorption.

DETD However, the fraction dose absorbed may be independent of the dissolution of the drug if the **solubility** is very low or the dose very high. This region, termed the **solubility** limited region of drug absorption, clearly indicates that the extent of drug absorption will be very dependent on the **solubility** of the drug in the gastro-intestinal luminal contents [Hernell et al., 1990; Staggers et al., 1990; and Davenport, 1982].

DETD . . . a more hydrophilic co-surfactant, that is, a co-surfactant with a high HLB number, not only increases the dissolution of poorly water-**soluble** drugs and pharmaceuticals but, that it also greatly increases the in vivo bioavailability of the poorly water-**soluble** drug or pharmaceutical. That is, not only is more of the poorly water-**soluble** drug or pharmaceutical **solubilized** but, the self-microemulsifying formulation of the present invention also presents the drug or pharmaceutical ingredient to an organism in a. . .

DETD . . . were prepared following the phase diagram of Farah et al. [1993]. Briefly nifedipine was added to a test tube and **solubilized** in a mixture of surfactant (75 µl LABRAFAC CM 10, Gattefosse Corporation, Westwood, N.J.), co-surfactant (175 µl LAUROGLYCOL, HLB=4 or. . . in both cases was a clear solution at this temperature. The solution was then added to a size 1, hard **gelatin** capsules (HGC, Capsugel) and allowed to cool. For the bulk powder formulation, nifedipine was weighed out and added to the hard **gelatin** capsules at the same dose as the lipid formulations.

DETD The results of these experiments showed that semi-solid lipid filled

hard **gelatin** capsules can be an effective method of improving the **oral** bioavailabiltiy of water insoluble drugs. A clear trend was shown in the improvement of the bioavailability of nifedipine in dogs. . . HLB (HLB=14) value over that of a co-surfactant with a low HLB (HLB=4) value even though both formulations appeared to **solubilize** the drug equally.

DETD Sarciaux et al. (1995) Using microemulsion formulations for **oral** drug delivery of therapeutic peptides. Int'l. Journal of Pharmaceutics, 120:127-136.

CLM What is claimed is:
12. A method as set forth in claim 8 further including the step of **solubilizing** the drug, surfactant, and co-surfactant in a solvent.

L16 ANSWER 4 OF 11 USPATFULL
Full-text

ACCESSION NUMBER:	1999:136721 USPATFULL
TITLE:	Method for making a multi-stage drug delivery system
INVENTOR(S):	Crison, John R., Ann Arbor, MI, United States **Amidon, Gordon L.**, Ann Arbor, MI, United States
PATENT ASSIGNEE(S):	Port Systems, L.L.C., Ann Arbor, MI, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5976571		19991102
APPLICATION INFO.:	US 1997-946515		19971007 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1995-383830, filed on 6 Feb 1995, now patented, Pat. No. US 5674530 which is a division of Ser. No. US 1994-251731, filed on 31 May 1994, now patented, Pat. No. US 5387421 which is a continuation of Ser. No. US 1992-826253, filed on 27 Jan 1992, now abandoned which is a continuation of Ser. No. US 1991-648968, filed on 31 Jan 1991, now abandoned

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Bawa, Raj
LEGAL REPRESENTATIVE:	Hudak & Shunk Co., L.P.A.
NUMBER OF CLAIMS:	29
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	13 Drawing Figure(s); 7 Drawing Page(s)
LINE COUNT:	1043

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A drug delivery system (10) includes a first capsule half (12) having an inner chamber (16) for containing a drug (18) therein. A plug (28) is disposed in a passageway (26) of the capsule half (12) for plugging the opening (24) thereof. The plug (28) is releasable from the passageway opening (24) upon the application of pressure from within the inner chamber (16). A pump mechanism, reactive with the external environment of the capsule half (12), causes an increase in pressure within the inner chamber (16) and forces the plug (28) out of the passageway (26) to release the drug (18) from the inner chamber (16) and out of the passageway (26). Thusly, after initial release of drug from a second capsule half (14) releasably mounted on the first capsule half (12), the first capsule half (12) provides a second pulse of drug release at a predetermined time after initial ingestion of the capsule. The invention further provides a method of manufacturing the drug delivery system (10) and method by which the drug delivery system (10) provides the drug to a body.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IN **Amidon, Gordon L.**, Ann Arbor, MI, United States

SUMM It has been recognized that there is a need for a drug delivery system which yields an increase in the **oral** dosing interval of drugs exhibiting presystemic loss metabolism while simultaneously maintaining bioavailability equivalent to the immediate release dosage form. Such drugs would otherwise either require short interval dosing, such as periodic **oral** dosing having short periods between each **oral** dosing.

SUMM . . . for emitting external fluid into the osmotic device. The device includes an opening having an erodible element, such as a **gelatin** plug that erodes and forms an osmotic passageway in the environment of use. Within the device is a modulating agent in nonequilibrium proportions. Upon the influx of fluid into the device, there is co-**solubilization** of a useful agent which is then released from the device. Thusly, co-**solubilization** of a modulating agent and a useful agent controls

the release of the useful agent and results in the delayed. . .

SUMM . . . of drug will escape metabolism and therefore be available. For those drugs with incomplete absorption due to low permeability, poor **solubility** or in which case the absorption rate limited by rate of dissolution, enhancers can be added to increase the bioavailability.. . .

DETD The capsule halves 12,14 can be made from various materials, preferably water containing **gelatins**.

DETD . . . checked from three spots in the mortar taking one gram sample. A 98.4% yield was obtained. A number zero hard **gelatin** two piece capsule was filled with 350 mg +/-1.5 mg of the fill mix or adjusted to give a potency. . .

DETD . . . +/-1 mg of the captopril immediate release blend (50%) was disposed into the cap of the size number zero hard **gelatin** and mounted onto the capsule previously referred to above. The cap was placed on the body taking care not to. . .

DETD . . . coating or immersion coating of the capsules 12 include acetone for water insoluble materials and water (H O) for water **soluble** coating materials. Other suitable solvents known to those skilled in the art can also be used.

DETD A number zero hard **gelatin** two piece capsule (Capsugel, Greenwood, S.C.) was filled with 200 mg of the osmotic charge (sorbitol/lactose)-aspirin formulation. Gelucire 50/02 was. . .

DETD Capsules, prepared as described above numbered from 3 to 7, were used for bioavailability study. Captopril tablets and powder for **oral** and intravenous studies were kindly donated by Squibb. Two male beagle dogs, weighing thirty-four and thirty pounds and two midgut-fistulated. . .

DETD **Oral** study--Four tablets containing 25 mg of Captopril were given to four dogs orally with 20 ml of tap water. Dogs. . .

DETD The study was duplicated in each dog. The experimental design was the same as the **oral** study except that the schedule for sample collection was every one hour for twelve to thirteen hours. Dogs were released. . .

DETD . . . time zero to infinity by extrapolating the last blood concentration with an elimination rate constant (ke) were evaluated from the **oral**, intravenous, and technology studies based on the noncompartmental analysis. Relative bioavailability of technology capsules were determined comparing to the **oral** study and normalized by the dose given.

DETD Size 0, hard **gelatin** capsules were coated with cellulose acetate which was dissolved in acetone and ethanol. Triacetin was used as a plasticizer. The. . .

DETD Caps were removed from size 2 hard **gelatin** capsules (Capsugel®) and the bodies were manually dipped into a (9% w/v acetone +1.4% w/v triacetin) solution of cellulose acetate. . .

DETD Size 1 hard **gelatin** capsules (Capsugel®) were dipped into a solution of 15 gm polyurethane (Spenkel F78-M-50, Reichold) in 30 gm of acetone, USP/NF. . .

DETD . . . USP
100.00
Lactose, Anhydrous, USP
41.00
Mictocrystalline Cellulose, NF
97.35
Sorbitol, NF 35.00
Croscarmellose Sodium, NF
7.00
Magnesium Stearate, BP
1.75
Gelocire 50/02 120.00
Size #0 hard **gelatin** two piece capsules
66.00
Captopril immediate release blend (50%)
Coating solution for captopril pulsatile
q.s. to obtain
release capsules suitable release

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* Microcrystalline. . .

L16 ANSWER 5 OF 11 USPATFULL
Full-text
ACCESSION NUMBER: 1998:159220 USPATFULL
TITLE: Water **soluble** pharmaceutical coating and method for producing coated pharmaceuticals
INVENTOR(S): **Amidon, Gordon L.**, Ann Arbor, MI, United States

	Crison, John R., Ann Arbor, MI, United States		
PATENT ASSIGNEE(S):	Port Systems, L.L.C., Ann Arbor, MI, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5851275		19981222
APPLICATION INFO.:	US 1997-790737		19970127 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1996-594814, filed on 31 Jan 1996, now patented, Pat. No. US 5686133		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Dudash, Diana		
LEGAL REPRESENTATIVE:	Kohn & Associates		
NUMBER OF CLAIMS:	5		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	10 Drawing Figure(s); 5 Drawing Page(s)		
LINE COUNT:	704		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of making a pharmaceutical composition is disclosed. The method includes the steps of contacting at least one pharmaceutical ingredient with a mixture consisting essentially of **gelatin** and lecithin to increase the dissolution rate of water-insoluble pharmaceutical ingredients. A pharmaceutical excipient coating for increasing the dissolution rate of water-insoluble pharmaceutical ingredients is also disclosed. The coating consists essentially of **gelatin** and lecithin.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Water **soluble** pharmaceutical coating and method for producing coated pharmaceuticals

IN **Amidon, Gordon L.**, Ann Arbor, MI, United States

AB . . . is disclosed. The method includes the steps of contacting at least one pharmaceutical ingredient with a mixture consisting essentially of **gelatin** and lecithin to increase the dissolution rate of water-insoluble pharmaceutical ingredients. A pharmaceutical excipient coating for increasing the dissolution rate of water-insoluble pharmaceutical ingredients is also disclosed. The coating consists essentially of **gelatin** and lecithin.

SUMM It is well known in the art that there are solid drugs which are scarcely **soluble** in water. Due to their low **solubilities**, these drugs have a correspondingly low degree of bioavailability.

SUMM Several prior art processes have been developed in efforts to increase the **solubility** and, hence, the bioavailability of poorly **soluble** pharmaceuticals or drugs. One such prior art process discloses the use of water-**soluble** high-molecular weight substances having low melting points, such as Carbowax, in combination with an insoluble drug. However, compositions prepared by. . .

SUMM Other methods of increasing the aqueous dissolution rate of poorly water-**soluble** drugs include the use of organic solvents to **solubilize** the poorly water-**soluble** drug or pharmaceutical composition. One such method is disclosed in U.S. Pat. No. 4,540,602 to Motoyama et al., issued Sep.. . . 10, 1985, which discloses a process for the preparation of activated pharmaceutical compositions containing a solid drug that is scarcely **soluble** in water. The method includes the steps of dissolving or **solubilizing** a solid drug, that is highly insoluble in water, in a low-boiling point hydrophobic organic solvent such as lecithin. The **solubilized** drug is then emulsified in the presence of a water-**soluble**, high-molecular weight substance, such as **gelatin**, and the drug is removed from the emulsion.

SUMM The method disclosed in the Motoyama et al. reference **solubilizes** the drug and then resolidifies/recrystalizes the drug in a water-**soluble** matrix such as **gelatin** or lecithin. The Motoyama et al. method requires the use of organic solvents in order to **solubilize** the drug. This method has several inherent disadvantages or drawbacks. First, since the drug is **solubilized** and then recrystalized, the recrystalized product must be reidentified since polymorphic changes can occur when the drug is recrystalized in. . . Additionally, since the compounds of interest in the Motoyama patent are water-insoluble, organic solvents must be used in order to **solubilize** the drugs of interest. The use of organic solvents creates further problems with the health and safety aspects of organic. . . the use of organic solvents considerably add to the cost of utilizing organic solvents in a method to increase the **solubility** of water-insoluble drugs as organic solvent recovery and containment devices are very costly. Other known surface active excipients can be. . .

SUMM Therefore, it would be advantageous and desirable to have a method of increasing the dissolution rate of poorly water-**soluble** pharmaceuticals which avoids the drawbacks of the prior art methods. Furthermore, it would be desirable to have a method which is completely aqueous-based in order to avoid the necessity for recharacterization of the pharmaceuticals or drugs according to the **solubilization** method disclosed above and also eliminating the cost and both health and environmental safety aspects of using organic solvents. It. . .

SUMM By combining the method and coating of the present invention with poorly water-**soluble** drugs or pharmaceutical compositions, optimal advantage can be taken of the potential potency and efficacy of poorly water-**soluble** drugs by increasing their bioavailability. The present invention provides an improved method and coating for providing poorly water-**soluble** drugs with a means for a greater dissolution rate and, hence, greater bioavailability which includes all of the aforementioned mentioned. . .

SUMM . . . a method of making a pharmaceutical composition by contacting at least one pharmaceutical ingredient with a mixture consisting essentially of **gelatin** and lecithin to increase the dissolution rate of water-insoluble pharmaceutical ingredients.

SUMM . . . provides a pharmaceutical excipient coating for increasing the dissolution rate of water-insoluble pharmaceutical ingredient wherein the coating consists essentially of **gelatin** and lecithin.

DRWD FIG. 1b is a plot of Do vs. DN for griseofulvin and digoxin which are drugs which have similar **solubilities** (0.017 mg/ml and 0.024 mg/ml, respectively) but have different absorption potentials due to the dose (500 mg vs. 0.5 mg);

DRWD FIG. 2 is a graph showing the dissolution profiles of bulk cyclosporin powder and bulk cyclosporin coated with the lecithin/**gelatin** coating according to the present invention in 0.01% sodium lauryl sulfate (SLS);

DRWD FIG. 3 is a graph showing the percent of bulk cyclosporin powder and bulk cyclosporin powder coated with the lecithin/**gelatin** coating according to the present invention dissolved in simulated intestinal fluid (SIP) at pH 7.5@37.degree. C.;

DRWD FIG. 5 is a graph showing dog plasma levels of cyclosporin bulk powder and cyclosporin bulk powder formulated with a lecithin/**gelatin** mixture according to the present invention after **oral** administration wherein the area under the curve (AUC) for the lecithin/**gelatin** coated formulation in two (2) times the AUC for the bulk powder;

DRWD FIG. 6 is a graph comparing bulk cyclosporin powder and lecithin/**gelatin** coated cyclosporin prepared by spray-drying onto Nu-Pareils®;

DRWD FIG. 7 is a graph showing percent cyclosporin dissolved comparing a lecithin/**gelatin** coated formulation according to the present invention with bulk cyclosporin powder in simulated intestinal fluid (SIF), USP, pH 7.5@37.degree. C.;

DRWD FIG. 8 is a graph showing the dissolution of lyophyllized lecithin/**gelatin** coated cyclosporin compared with bulk cyclosporin powder; in Milli:-Q water@37.degree. C.

DETD . . . ingredients is disclosed. The method generally includes the steps of contacting at least one pharmaceutical ingredient with a mixture including **gelatin** and lecithin.

DETD . . . pharmaceutical ingredient at a time can be treated according to the present invention to yield a desired pharmaceutical composition. Additionally, poorly-water-**soluble** pharmaceutical ingredients can be treated according to the present invention and can then be used in combination with other pharmaceutical ingredients which therefore may or may not be poorly water-**soluble**.

DETD The method includes the steps of dissolving **gelatin** in water heated to between 35°-40° C. Lecithin is added to the **gelatin**/water mixture and is thoroughly mixed therein. At least one pharmaceutical ingredient in solid particulate form is then added slowly and. . . mixed so as to cause thorough and uniform coating of the particles of the pharmaceutical ingredient. Following coating with the **gelatin**/lecithin mixture, the coated pharmaceutical ingredient is then dried.

DETD Referring to Table 1, the general range of concentrations of excipient (i.e., the lecithin/**gelatin**) and pharmaceutical ingredient is shown. The concentration in the coating solution of **gelatin** and lecithin broadly ranges from approximately 0.001-99.90 (w/v) each and more preferably 0.01 to 2.0% each. The concentration in the coating solution of the pharmaceutical ingredient ranges from approximately 0.1-15.0% (w/v). It is preferable that the lecithin and **gelatin** be present in a 1:1 ratio.

DETD The contacting step includes coating the pharmaceutical ingredient with

the mixture including water **gelatin** and lecithin. The coating step can be accomplished by simple immersion of the particles of the pharmaceutical ingredient. It is believed that the **gelatin** coats the particles of the pharmaceutical ingredient and prevents aggregation or clumping of the particles. The lecithin element is thought. . . or to form micelles which facilitate dissolution of the pharmaceutical ingredient. In acting in this complementary fashion, the coating including **gelatin** and lecithin increases the dissolution rate of water-insoluble pharmaceutical ingredients. The above-described theory is provided merely for descriptive purposes and. . .

DETD After the pharmaceutical ingredient(s) is coated with the aqueous mixture of **gelatin** and lecithin, the aqueous solvent water can be removed by various techniques.

DETD . . . The basic design consists of a spray nozzle, a drying chamber, and an air source. The drug, along with other **solubilized** or suspended materials are pumped through a spray nozzle, atomized and dried into a fine, amorphous powder. Alternatively, it is. . .

DETD Additionally, the method of the present invention can include the step of spray coating the **gelatin**/lecithin coated pharmaceutical ingredient onto micronized particles. Micronization is the process by which solid drug particles are reduced in size as. . . equation 1; ##EQU1## where m is the mass of drug, t is time, SA is surface area, C is the **solubility** of the drug, h is the diffusional boundary layer thickness, and C is the concentration of drug in the bulk. . .

DETD . . . active pharmaceutical ingredient utilized in the method of the present invention can include griseofulvin, cyclosporin (see Table 3 for aqueous **solubilities** of these compounds and other suitable pharmaceutical ingredients or drugs having low water **solubility**).

DETD Referring to FIG. 2, initial dissolution rates for cyclosporin formulations are shown. The dissolution rate for cyclosporin coated with lecithin/**gelatin** was shown to be greater than for bulk cyclosporin powder.

DETD . . . initial dissolution rates and the total dissolution rates over time were greater for both cyclosporin and griseofulvin treated with the lecithin/**gelatin** coating of the present invention than with the non-coated formulations tested. The results illustrate for both cyclosporin and griseofulvin that. . . rates of dissolution and the dissolution over time were both faster and greater when each compound was treated with the lecithin/**gelatin** coating. Additionally, the results shown in these Figures demonstrate that cyclosporin treated with the lecithin/**gelatin** coating of the present invention had both a greater initial dissolution rate and a greater dissolution rate over time than bulk cyclosporin powder. The same results were true for the griseofulvin treated with the lecithin/**gelatin** coating of the present invention, that is, the griseofulvin treated with the lecithin/**gelatin** coating demonstrated both a greater initial dissolution rate and a greater overall percentage of dissolution over time as compared to. . .

DETD . . . cyclosporin formulations are illustrated. Table 2 illustrates a doubling of the relative bioavailability of cyclosporin given orally in dogs for lecithin/**gelatin** coated cyclosporin versus bulk cyclosporin powder.

DETD . . . the fraction dose absorbed is inversely proportional to dose and is directly proportion to the dissolution rate. Therefore, in vivo **solubilization** and dissolution are important determinants of drug absorption.

DETD . . . addition to the symbols defined previously, M is the dose, and r is the initial particle radius, C is the **solubility**, p is the density, Pff is the effective permeability, tes is the residence time, tbs is the absorption time, and. . .

DETD where C is the **solubility** of the drug, and C (0) is the concentration of the drug entering the intestine.

DETD The class of drugs that are being considered in this patent are those that have low **solubility**, i.e., drugs where the concentration greatly exceeds the **solubility**. The absorption of these drugs is limited by how much drug can get into solution. According to the Hixson-Crowell cube. . . percent of drug in solution in a given period of time is a function of the particle size and the **solubility**. ##EQU5## Where D, C, r, t and p are previously defined. In the case of water insoluble drugs, the **solubility**, or C is low such that the dose of drug given exceeds the amount of fluids available in the GI tract for complete dissolution to take place. Therefore, reducing the particle size or increasing the **solubility**, or both, are methods for increasing the dissolution rate and absorption of a water insoluble drug.

DETD The second disadvantage comes from attempting to increase the **solubility**. Two methods can be used to increase the **solubility** of a drug, 1) formation of a salt, and 2) incorporating surfactants in the formulation. Salt formation has been used successfully but is limited to weak acids and bases. In theory, surfactants should work well to increase the **solubility**, however the concentration of surfactants needed to overcome the dilution effect of the GI tract often exceeds safe levels. Since. . .

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DETD FIGS. 2 and 3 show the dissolution profile of cyclosporin bulk powder, with and without the lecithin/**gelatin** coating in 0.01% sodium lauryl sulfate and Simulated Intestinal Fluid, pH 7.5 at 37° C. In the surfactant solution, 17% of the lecithin/**gelatin** formulation was in solution after 120 minutes compared to the bulk powder which was 3.4% in solution in the same. . .

DETD . . . used in the in vitro experiments was administered to dogs both as the bulk powder and formulated with lecithin and **gelatin** as described above. The lecithin/**gelatin** formulation and bulk powder were suspended in 10 ml of water administered via a gastric tube followed by 40 ml. . . content. FIG. 5 shows the results of this study (Abdallah and Mayersohn, 1991; (Bowers, 1990]. Based on these results, the lecithin/**gelatin** formulation showed a 2.0-fold increase in bioavailability relative to the bulk powder.

DETD FIG. 5 illustrates the results of a study performed to determine the relative plasma concentration of cyclosporin over time following **oral** administration. The data illustrated in FIG. 6 suggests that coated cyclosporin powder was more readily dissolved into the intestinal lumen. . .

DETD As was stated above, the method of the present invention can include the manufacture of pharmaceutical ingredients treated with the lecithin/**gelatin** coating which is then lyophilized or the pharmaceutical ingredient treated with the lecithin/**gelatin** coating can be spray coated onto beads. Referring to FIG. 8, lyophilized cyclosporin formulation treated with the lecithin/**gelatin** coating and bulk cyclosporin powder were compared. The percentage cyclosporin dissolved in Milli-Q (Millipore, Corp.) (deionized, distilled water) over time is illustrated. The lyophilized cyclosporin coated with lecithin/**gelatin** demonstrated both a greater initial dissolution rate and greater overall percentage dissolution of coated cyclosporin as compared to the bulk. . .

DETD . . . order to ascertain in vitro data regarding the performance of the subject invention. Cyclosporin, a immunosuppressive drug, has an aqueous **solubility** of about 0.006 mg/ml. This compound was formulated with lecithin and **gelatin**, as described above, and its dissolution into 0.25% sodium lauryl sulfate was measured as shown in FIG. 2. The lecithin/**gelatin** formulation and the bulk powder form were treated in Simulated Intestinal Fluid, USP for two hours with 0.25% w/v sodium. . .

DETD As shown in FIGS. 3 and 8, in the simulated intestinal fluid, the amount dissolved of the lecithin/**gelatin** coated formulation was much greater than bulk powder which was essentially insoluble over the cause of the experiment.

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DETD The results of the above studies demonstrate that the lecithin/**gelatin** coating of the present invention greatly increases both the initial dissolution rate and total percentage dissolution of previously poorly water-**soluble** pharmaceutical ingredients. That is, the method of coating a poorly water-**soluble** pharmaceutical ingredient with a pharmaceutical excipient or coating formulation which includes lecithin and **gelatin** greatly increased both the initial dissolution rate and overall percent dissolution of the previously poorly water-**soluble** pharmaceutical ingredient. The increased dissolution of the pharmaceutical ingredients treated according to the present invention allows drugs which may have poor water-**solubility** to be utilized since the method and coating of the present invention greatly increases the dissolution rate of these poorly water-**soluble** pharmaceuticals contained therein.

DETD . . . been shown to function in vitro as well as in vivo. The present invention increases the dissolution rate of poorly water-**soluble** pharmaceutical ingredients without **solubilizing** and/or then recrystalizing the pharmaceutical ingredient thereby eliminating the necessity for recharacterization or reidentification the pharmaceutical ingredient as discussed above. . .

DETD TABLE 1

Range of lecithin and **gelatin** (% weight of final powder) = 1% to 40% (w/w).

Material	Range of Conc. in Coating Solution (% w/v)
lecithin	0.01-2.0
gelatin	0.01-2.0
drug	0.1-12

DETD TABLE 2

Relative Bioavailability in Dogs of Cyclosporin Given **Oral** Comparing the Lecithin/**Gelatin** formulation with the Bulk Powder

Formulation	AUC-6 (μg-hr/ml)	Relative Increase in Bioavailabilty
cyclosporin bulk powder	0.7	1.0
lecithin/**gelatin** cyclosporin formulation	1.4	2.0

DETD TABLE 3

Examples of Currently Marketed Water Insoluble Drugs

Formulation	**Solubility** (mg/ml)	Dose (mg)	VISSOLUTION (liters)
Cyclosporin1	0.006	750	125
Griseofulvin2	0.017	500	29.4
Digoxin3	0.024	0.50	0.021
Nifedipine4	0.010	30.0	3.0
Itraconozole5	0.001	200	9.9
Carbamazepine6			

. . . Steimer, and W. Niederberger, J. Pharmacokinet, Biophar. 16:331-353 (1988).

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DETD Grant and Higuchi, in Techniques of Chemistry, "**Solubility** Behaviour of Organic Compounds", Volume 21, W. H. Saunders, Editor, John Wiley & Sons, Toronto, Canada (1990).

DETD Oh et al, "Estimating the Fraction Dose Absorbed from Suspensions of Poorly **Soluble** Compounds in Humans: A Mathematical Model. Pharm Res, 10: 264-270 (1993).

CLM What is claimed is:

1. A pharmaceutical excipient coating for increasing the dissolution rate of water-insoluble pharmaceutical ingredients, said coating consisting essentially of **gelatin** and lecithin in a non-bilayer form.

2. A coating according to claim 1, wherein the concentration of said **gelatin** component ranges from 0.001% (w/v) to 99.9% (w/v).

3. A coating according to claim 2, wherein the concentration of said **gelatin** component ranges from 0.01% (w/v) to 2.0% (w/v).

L16 ANSWER 6 OF 11 USPATFULL

Full-text

ACCESSION NUMBER: 1998:138474 USPATFULL

TITLE: Water **soluble** pharmaceutical coating and method for producing coated pharmaceuticals

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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of making a pharmaceutical composition is disclosed. The method includes the steps of contacting at least one pharmaceutical ingredient with a mixture consisting essentially of **gelatin** and lecithin to increase the dissolution rate of water-insoluble pharmaceutical ingredients. A pharmaceutical excipient coating for increasing the dissolution rate of water-insoluble pharmaceutical ingredients is also disclosed. The coating consists essentially of **gelatin** and lecithin.

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SUMM It is well known in the art that there are solid drugs which are scarcely **soluble** in water. Due to their low **solubilities**, these drugs have a correspondingly low degree of bioavailability.

SUMM Several prior art processes have been developed in efforts to increase the **solubility** and, hence, the bioavailability of poorly **soluble** pharmaceuticals or drugs. One such prior art process discloses the use of water-**soluble** high-molecular weight substances having low melting points, such as Carbowax, in combination with an insoluble drug. However, compositions prepared by. . .

SUMM Other methods of increasing the aqueous dissolution rate of poorly water-**soluble** drugs include the use of organic solvents to

solubilize the poorly water-**soluble** drug or pharmaceutical composition. One such method is disclosed in U.S. Pat. No. 4,540,602 to Motoyama et al., issued Sep.. . . 10, 1985, which discloses a process for the preparation of activated pharmaceutical compositions containing a solid drug that is scarcely **soluble** in water. The method includes the steps of dissolving or **solubilizing** a solid drug, that is highly insoluble in water, in a low-boiling point hydrophobic organic solvent such as lecithin. The **solubilized** drug is then emulsified in the presence of a water-**soluble**, high-molecular weight substance, such as **gelatin**, and the drug is removed from the emulsion.

SUMM The method disclosed in the Motoyama et al. reference **solubilizes** the drug and then resolidifies/recrystalizes the drug in a water-**soluble** matrix such as **gelatin** or lecithin. The Motoyama et al. method requires the use of organic solvents in order to **solubilize** the drug. This method has several inherent disadvantages or drawbacks. First, since the drug is **solubilized** and then recrystalized, the recrystalized product must be reidentified since polymorphic changes can occur when the drug is recrystalized in. . . Additionally, since the compounds of interest in the Motoyama patent are water-insoluble, organic solvents must be used in order to **solubilize** the drugs of interest. The use of organic solvents creates further problems with the health and safety aspects of organic. . . the use of organic solvents considerably add to the cost of utilizing organic solvents in a method to increase the **solubility** of water-insoluble drugs as organic solvent recovery and containment devices are very costly. Other known surface active excipients can be. . .

SUMM Therefore, it would be advantageous and desirable to have a method of increasing the dissolution rate of poorly water-**soluble** pharmaceuticals which avoids the drawbacks of the prior art methods. Furthermore, it would be desirable to have a method which is completely aqueous-based in order to avoid the necessity for recharacterization of the pharmaceuticals or drugs according to the **solubilization** method disclosed above and also eliminating the cost and both health and environmental safety aspects of using organic solvents. It. . .

SUMM By combining the method and coating of the present invention with poorly water-**soluble** drugs or pharmaceutical compositions, optimal advantage can be taken of the potential potency and efficacy of poorly water-**soluble** drugs by increasing their bioavailability. The present invention provides an improved method and coating for providing poorly water-**soluble** drugs with a means for a greater dissolution rate and, hence, greater bioavailability which includes all of the aforementioned mentioned. . .

SUMM . . . a method of making a pharmaceutical composition by contacting at least one pharmaceutical ingredient with a mixture consisting essentially of **gelatin** and lecithin to increase the dissolution rate of water-insoluble pharmaceutical ingredients.

SUMM . . . provides a pharmaceutical excipient coating for increasing the dissolution rate of water-insoluble pharmaceutical ingredient wherein the coating consists essentially of **gelatin** and lecithin.

DRWD FIG. 1b is a plot of Do vs. DN for griseofulvin and digoxin which are drugs which have similar **solubilities** (0.017 mg/ml and 0.024 mg/ml, respectively) but have different absorption potentials due to the dose (500 mg vs. 0.5 mg);

DRWD FIG. 2 is a graph showing the dissolution profiles of bulk cyclosporin powder and bulk cyclosporin coated with the lecithin/**gelatin** coating according to the present invention in 0.01% sodium lauryl sulfate (SLS);

DRWD FIG. 3 is a graph showing the percent of bulk cyclosporin powder and bulk cyclosporin powder coated with the lecithin/**gelatin** coating according to the present invention dissolved in simulated intestinal fluid (SIP) at pH 7.5 @ 37° C.;

DRWD FIG. 5 is a graph showing dog plasma levels of cyclosporin bulk powder and cyclosporin bulk powder formulated with a lecithin/**gelatin** mixture according to the present invention after **oral** administration wherein the area under the curve (AUC) for the lecithin/**gelatin** coated formulation in two (2) times the AUC for the bulk powder;

DRWD FIG. 6 is a graph comparing bulk cyclosporin powder and lecithin/**gelatin** coated cyclosporin prepared by spray-drying onto Nu-Pareils®;

DRWD FIG. 7 is a graph showing percent cyclosporin dissolved comparing a lecithin/**gelatin** coated formulation according to the present invention with bulk cyclosporin powder in simulated intestinal fluid (SIF), USP, pH 7.5 @. . .

DRWD FIG. 8 is a graph showing the dissolution of lyophyllized lecithin/**gelatin** coated cyclosporin compared with bulk cyclosporin powder; in Milli:-Q water @ 37° C.

DETD . . . ingredients is disclosed. The method generally includes the steps of contacting at least one pharmaceutical ingredient with a mixture including **gelatin** and lecithin.

DETD . . . pharmaceutical ingredient at a time can be treated according to the present invention to yield a desired pharmaceutical composition. Additionally, poorly-water-**soluble** pharmaceutical ingredients can be treated according to the present invention and can then be used in combination with other pharmaceutical ingredients which therefore may or may not be poorly water-**soluble**.

DETD The method includes the steps of dissolving **gelatin** in water heated to between 35°-40° C. Lecithin is added to the **gelatin**/water mixture and is thoroughly mixed therein. At least one pharmaceutical ingredient in solid particulate form is then added slowly and. . . mixed so as to cause thorough and uniform coating of the particles of the pharmaceutical ingredient. Following coating with the **gelatin**/lecithin mixture, the coated pharmaceutical ingredient is then dried.

DETD Referring to Table 1, the general range of concentrations of excipient (i.e., the lecithin/**gelatin**) and pharmaceutical ingredient is shown. The concentration in the coating solution of **gelatin** and lecithin broadly ranges from approximately 0.001-99.9% (w/v) each and more preferably 0.01% to 2.0% each. The concentration in the coating solution of the pharmaceutical ingredient ranges from approximately 0.1-15.0% (w/v). It is preferable that the lecithin and **gelatin** be present in a 1:1 ratio.

DETD The contacting step includes coating the pharmaceutical ingredient with the mixture including water **gelatin** and lecithin. The coating step can be accomplished by simple immersion of the particles of the pharmaceutical ingredient. It is believed that the **gelatin** coats the particles of the pharmaceutical ingredient and prevents aggregation or clumping of the particles. The lecithin element is thought. . . or to form micelles which facilitate dissolution of the pharmaceutical ingredient. In acting in this complementary fashion, the coating including **gelatin** and lecithin increases the dissolution rate of water-insoluble pharmaceutical ingredients. The above-described theory is provided merely for descriptive purposes and. . .

DETD After the pharmaceutical ingredient(s) is coated with the aqueous mixture of **gelatin** and lecithin, the aqueous solvent water can be removed by various techniques.

DETD . . . The basic design consists of a spray nozzle, a drying chamber, and an air source. The drug, along with other **solubilized** or suspended materials are pumped through a spray nozzle, atomized and dried into a fine, amorphous powder. Alternatively, it is. . .

DETD Additionally, the method of the present invention can include the step of spray coating the **gelatin**/lecithin coated pharmaceutical ingredient onto micronized particles. Micronization is the process by which solid drug particles are reduced in size. Since. . .

DETD . . . equation 1; ##EQU1## where m is the mass of drug, t is time, SA is surface area, C is the **solubility** of the drug, h is the diffusional boundary layer thickness, and C is the concentration of drug in the bulk. . .

DETD . . . active pharmaceutical ingredient utilized in the method of the present invention can include griseofulvin, cyclosporin (see Table 3 for aqueous **solubilities** of these compounds and other suitable pharmaceutical ingredients or drugs having low water **solubility**).

DETD Referring to FIG. 2, initial dissolution rates for cyclosporin formulations are shown. The dissolution rate for cyclosporin coated with lecithin/**gelatin** was shown to be greater than for bulk cyclosporin powder.

DETD . . . initial dissolution rates and the total dissolution rates over time were greater for both cyclosporin and griseofulvin treated with the lecithin/**gelatin** coating of the present invention than with the non-coated formulations tested. The results illustrate for both cyclosporin and griseofulvin that. . . rates of dissolution and the dissolution over time were both faster and greater when each compound was treated with the lecithin/**gelatin** coating. Additionally, the results shown in these Figures demonstrate that cyclosporin treated with the lecithin/**gelatin** coating of the present invention had both a greater initial dissolution rate and a greater dissolution rate over time than bulk cyclosporin powder. The same results were true for the griseofulvin treated with the lecithin/**gelatin** coating of the present invention, that is, the griseofulvin treated with the lecithin/**gelatin** coating demonstrated both a greater initial dissolution rate and a greater overall percentage of dissolution over time as compared to. .

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DETD FIGS. 2 and 3 show the dissolution profile of cyclosporin bulk powder, with and without the lecithin/**gelatin** coating in 0.01% sodium lauryl sulfate and Simulated Intestinal Fluid, pH 7.5 at 37° C. In the surfactant solution, 17% of the lecithin/**gelatin** formulation was in solution after 120 minutes compared to the bulk powder which was 3.4% in solution in the same. . .

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drug	0.1-12

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Formulation	AUC-6 (μg-hr/ml)	Relative Increase in Bioavailability
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formulation

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DETD Oh et al, "Estimating the Fraction Dose Absorbed from Suspensions of Poorly **Soluble** Compounds in Humans: A Mathematical Model. Pharm Res, 10:264-270 (1993)

CLM What is claimed is:

. . . with a coating made by the method of contacting at least one pharmaceutical ingredient with a mixture consisting essentially of **gelatin** in a range of 0.01% (w/v) to 2.0% (w/v) and lecithin in a range of 0.001% (w/v) to 99.9% (w/v). . .

2. A pharmaceutical composition as set forth in claim 1, wherein said concentration of said **gelatin** component ranges from 0.01% (w/v) to 2.0% (w/v).

L16 ANSWER 7 OF 11 USPATFULL

Full-text

ACCESSION NUMBER: 97:104165 USPATFULL

TITLE: Water **soluble** pharmaceutical coating and method for producing coated pharmaceuticals

INVENTOR(S): **Amidon, Gordon L.**, Ann Arbor, MI, United States
Crison, John R., Ann Arbor, MI, United States

PATENT ASSIGNEE(S): Port Systems, L.L.C., Ann Arbor, MI, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5686133		19971111
APPLICATION INFO.:	US 1996-594814		19960131 (8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Dudash, Diana
LEGAL REPRESENTATIVE: Kohn & Associates
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 681

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of making a pharmaceutical composition is disclosed. The method includes the steps of contacting at least one pharmaceutical ingredient with a mixture consisting essentially of **gelatin** and lecithin to increase the dissolution rate of water-insoluble pharmaceutical ingredients. A pharmaceutical excipient coating for increasing the

dissolution rate of water-insoluble pharmaceutical ingredients is also disclosed. The coating consists essentially of **gelatin** and lecithin.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Water **soluble** pharmaceutical coating and method for producing coated pharmaceuticals

IN **Amidon, Gordon L.**, Ann Arbor, MI, United States

AB . . . is disclosed. The method includes the steps of contacting at least one pharmaceutical ingredient with a mixture consisting essentially of **gelatin** and lecithin to increase the dissolution rate of water-insoluble pharmaceutical ingredients. A pharmaceutical excipient coating for increasing the dissolution rate of water-insoluble pharmaceutical ingredients is also disclosed. The coating consists essentially of **gelatin** and lecithin.

SUMM It is well known in the art that there are solid drugs which are scarcely **soluble** in water. Due to their low **solubilities**, these drugs have a correspondingly low degree of bioavailability.

SUMM Several prior art processes have been developed in efforts to increase the **solubility** and, hence, the bioavailability of poorly **soluble** pharmaceuticals or drugs. One such prior art process discloses the use of water-**soluble** high-molecular weight substances having low melting points, such as Carbowax, in combination with an insoluble drug. However, compositions prepared by. . .

SUMM Other methods of increasing the aqueous dissolution rate of poorly water-**soluble** drugs include the use of organic solvents to **solubilize** the poorly water-**soluble** drug or pharmaceutical composition. One such method is disclosed in U.S. Pat. No. 4,540,602 to Motoyama et al., issued Sep.. . . 10, 1985, which discloses a process for the preparation of activated pharmaceutical compositions containing a solid drug that is scarcely **soluble** in water. The method includes the steps of dissolving or **solubilizing** a solid drug, that is highly insoluble in water, in a low-boiling point hydrophobic organic solvent such as lecithin. The **solubilized** drug is then emulsified in the presence of a water-**soluble**, high-molecular weight substance, such as **gelatin**, and the drug is removed from the emulsion.

SUMM The method disclosed in the Motoyama et al. reference **solubilizes** the drug and then resolidifies/recrystalizes the drug in a water-**soluble** matrix such as **gelatin** or lecithin. The Motoyama et al. method requires the use of organic solvents in order to **solubilize** the drug. This method has several inherent disadvantages or drawbacks. First, since the drug is **solubilized** and then recrystalized, the recrystalized product must be reidentified since polymorphic changes can occur when the drug is recrystalized in. . . Additionally, since the compounds of interest in the Motoyama patent are water-insoluble, organic solvents must be used in order to **solubilize** the drugs of interest. The use of organic solvents creates further problems with the health and safety aspects of organic. . . the use of organic solvents considerably add to the cost of utilizing organic solvents in a method to increase the **solubility** of water-insoluble drugs as organic solvent recovery and containment devices are very costly. Other known surface active excipients can be. . .

SUMM Therefore, it would be advantageous and desirable to have a method of increasing the dissolution rate of poorly water-**soluble** pharmaceuticals which avoids the drawbacks of the prior art methods. Furthermore, it would be desirable to have a method which is completely aqueous-based in order to avoid the necessity for recharacterization of the pharmaceuticals or drugs according to the **solubilization** method disclosed above and also eliminating the cost and both health and environmental safety aspects of using organic solvents. It. . .

SUMM By combining the method and coating of the present invention with poorly water-**soluble** drugs or pharmaceutical compositions, optimal advantage can be taken of the potential potency and efficacy of poorly water-**soluble** drugs by increasing their bioavailability. The present invention provides an improved method and coating for providing poorly water-**soluble** drugs with a means for a greater dissolution rate and, hence, greater bioavailability which includes all of the aforementioned mentioned. . .

SUMM . . . a method of making a pharmaceutical composition by contacting at least one pharmaceutical ingredient with a mixture consisting essentially of **gelatin** and lecithin to increase the dissolution rate of water-insoluble pharmaceutical ingredients.

SUMM . . . provides a pharmaceutical excipient coating for increasing the dissolution rate of water-insoluble pharmaceutical ingredient wherein the coating consists essentially of **gelatin** and lecithin.

DRWD FIG. 1b is a plot of Do vs. DN for griseofulvin and digoxin which are

drugs which have similar **solubilities** (0.017 mg/ml and 0.024 mg/ml, respectively) but have different absorption potentials due to the dose (500 mg vs. 0.5 mg);

DRWD FIG. 2 is a graph showing the dissolution profiles of bulk cyclosporin powder and bulk cyclosporin coated with the lecithin/**gelatin** coating according to the present invention in 0.01% sodium lauryl sulfate (SLS);

DRWD FIG. 3 is a graph showing the percent of bulk cyclosporin powder and bulk cyclosporin powder coated with the lecithin/**gelatin** coating according to the present invention dissolved in simulated intestinal fluid (SIP) at pH 7.5 @ 37° C.;

DRWD FIG. 5 is a graph showing dog plasma levels of cyclosporin bulk powder and cyclosporin bulk powder formulated with a lecithin/**gelatin** mixture according to the present invention after **oral** administration wherein the area under the curve (AUC) for the lecithin/**gelatin** coated formulation in two (2) times the AUC for the bulk powder;

DRWD FIG. 6 is a graph comparing bulk cyclosporin powder and lecithin/**gelatin** coated cyclosporin prepared by spray-drying onto Nu-Pareils®;

DRWD FIG. 7 is a graph showing percent cyclosporin dissolved comparing a lecithin/**gelatin** coated formulation according to the present invention with bulk cyclosporin powder in simulated intestinal fluid (SIF), USP, pH 7.5 @. . .

DRWD FIG. 8 is a graph showing the dissolution of lyophyllized lecithin/**gelatin** coated cyclosporin compared with bulk cyclosporin powder; in Milli:-Q water @ 37° C.; and

DETD . . . ingredients is disclosed. The method generally includes the steps of contacting at least one pharmaceutical ingredient with a mixture including **gelatin** and lecithin.

DETD . . . pharmaceutical ingredient at a time can be treated according to the present invention to yield a desired pharmaceutical composition. Additionally, poorly-water-**soluble** pharmaceutical ingredients can be treated according to the present invention and can then be used in combination with other pharmaceutical ingredients which therefore may or may not be poorly water-**soluble**.

DETD The method includes the steps of dissolving **gelatin** in water heated to between 35°-40° C. Lecithin is added to the **gelatin**/water mixture and is thoroughly mixed therein. At least one pharmaceutical ingredient in solid particulate form is then added slowly and. . . mixed so as to cause thorough and uniform coating of the particles of the pharmaceutical ingredient. Following coating with the **gelatin**/lecithin mixture, the coated pharmaceutical ingredient is then dried.

DETD Referring to Table 1, the general range of concentrations of excipient (i.e., the lecithin/**gelatin**) and pharmaceutical ingredient is shown. The concentration in the coating solution of **gelatin** and lecithin broadly ranges from approximately 0.001-99.9% (w/v) each and more preferably 0.01% to 2.0% each. The concentration in the coating solution of the pharmaceutical ingredient ranges from approximately 0.1-15.0% (w/v). It is preferable that the lecithin and **gelatin** be present in a 1:1 ratio.

DETD The contacting step includes coating the pharmaceutical ingredient with the mixture including water **gelatin** and lecithin. The coating step can be accomplished by simple immersion of the particles of the pharmaceutical ingredient. It is believed that the **gelatin** coats the particles of the pharmaceutical ingredient and prevents aggregation or clumping of the particles. The lecithin element is thought. . . or to form micelles which facilitate dissolution of the pharmaceutical ingredient. In acting in this complementary fashion, the coating including **gelatin** and lecithin increases the dissolution rate of water-insoluble pharmaceutical ingredients. The above-described theory is provided merely for descriptive purposes and. . .

DETD After the pharmaceutical ingredient(s) is coated with the aqueous mixture of **gelatin** and lecithin, the aqueous solvent water can be removed by various techniques.

DETD . . . The basic design consists of a spray nozzle, a drying chamber, and an air source. The drug, along with other **solubilized** or suspended materials are pumped through a spray nozzle, atomized and dried into a fine, amorphous powder. Alternatively, it is. . .

DETD Additionally, the method of the present invention can include the step of spray coating the **gelatin**/lecithin coated pharmaceutical ingredient onto micronized particles. Micronization is the process by which solid drug particles are reduced in size as. . . equation 1; ##EQU1## where m is the mass of drug, t is time, SA is surface area, C is the **solubility** of the drug, h is the diffusional boundary layer thickness, and C is the concentration of drug in the bulk. . .

DETD . . . active pharmaceutical ingredient utilized in the method of the present invention can include griseofulvin, cyclosporin (see Table 3 for aqueous **solubilities** of these compounds and other suitable pharmaceutical ingredients or drugs having low water **solubility**).

DETD Referring to FIG. 2, initial dissolution rates for cyclosporin formulations are shown. The dissolution rate for cyclosporin coated with lecithin/**gelatin** was shown to be greater than for bulk cyclosporin powder.

DETD . . . initial dissolution rates and the total dissolution rates over time were greater for both cyclosporin and griseofulvin treated with the lecithin/**gelatin** coating of the present invention than with the non-coated formulations tested. The results illustrate for both cyclosporin and griseofulvin that. . . rates of dissolution and the dissolution over time were both faster and greater when each compound was treated with the lecithin/**gelatin** coating. Additionally, the results shown in these Figures demonstrate that cyclosporin treated with the lecithin/**gelatin** coating of the present invention had both a greater initial dissolution rate and a greater dissolution rate over time than bulk cyclosporin powder. The same results were true for the griseofulvin treated with the lecithin/**gelatin** coating of the present invention, that is, the griseofulvin treated with the lecithin/**gelatin** coating demonstrated both a greater initial dissolution rate and a greater overall percentage of dissolution over time as compared to. . .

DETD . . . cyclosporin formulations are illustrated. Table 2 illustrates a doubling of the relative bioavailability of cyclosporin given orally in dogs for lecithin/**gelatin** coated cyclosporin versus bulk cyclosporin powder.

DETD . . . the fraction dose absorbed is inversely proportional to dose and is directly proportion to the dissolution rate. Therefore, in vivo **solubilization** and dissolution are important determinants of drug absorption. Intestinal Drug Absorption--Theoretical Considerations Membrane Permeability and Luminal/Wall Concentration

DETD . . . addition to the symbols defined previously, M is the dose, and r is the initial particle radius, C is the **solubility**, ρ is the density, Pff is the effective permeability, tres is the residence time, tbs is the absorption time, and. . .

DETD where C is the **solubility** of the drug, and C (O) is the concentration of the drug entering the intestine.

DETD The class of drugs that are being considered in this patent are those that have low **solubility**, i.e., drugs where the concentration greatly exceeds the **solubility**. The absorption of these drugs is limited by how much drug can get into solution. According to the Hixson-Crowell cube. . . percent of drug in solution in a given period of time is a function of the particle size and the **solubility**. ##EQU5## Where D, C,r,t and ρ are previously defined. In the case of water insoluble drugs, the **solubility**, or C is low such that the dose of drug given exceeds the amount of fluids available in the GI tract for complete dissolution to take place. Therefore, reducing the particle size or increasing the **solubility**, or both, are methods for increasing the dissolution rate and absorption of a water insoluble drug.

DETD The second disadvantage comes from attempting to increase the **solubility**. Two methods can be used to increase the **solubility** of a drug, 1) formation of a salt, and 2) incorporating surfactants in the formulation. Salt formation has been used successfully but is limited to weak acids and bases. In theory, surfactants should work well to increase the **solubility**, however the concentration of surfactants needed to overcome the dilution effect of the GI tract often exceeds safe levels. Since. . .

DETD . . . for complete dissolution greatly exceed the fluid initially available. The brevity of this list confirms the importance of a drugs **solubility** to achieving a successful, marketable product.

DETD The significance of **solubility** and dissolution rate to absorption are clearly defined in the dose and dissolution numbers. More precisely, the dissolution rate is. . . on dose and dissolution is also noteworthy since it emphasizes that it is the dose number rather than just the **solubility**, that needs to be included in predicting drug absorption. Other physical constants such as diffusivity and particle density contribute to. . .

DETD Cyclosporin, an immunosuppressive drug with an aqueous **solubility** of 0.006 mg/ml at 37° C., was coated with lecithin and **gelatin** as described above. The lecithin/**gelatin** formula was prepared by dissolving 1 gm each of **gelatin**, USP/NF and lecithin NF in 100 ml of water. 0.5 gm of cyclosporin was added to this liquid and mixed. . .

DETD FIGS. 2 and 3 show the dissolution profile of cyclosporin bulk powder, with and without the lecithin/**gelatin** coating in 0.01% sodium lauryl sulfate and Simulated Intestinal Fluid, pH 7.5 at 37° C. In the surfactant solution, 17% of the lecithin/**gelatin** formulation was in solution after 120 minutes compared to the bulk powder which was 3.4% in solution in the same. . .

DETD . . . used in the in vitro experiments was administered to dogs both as the bulk powder and formulated with lecithin and **gelatin** as described above. The lecithin/**gelatin** formulation and bulk powder were suspended in 10 ml of water administered via a gastric tube followed by 40 ml. . . content. FIG. 5 shows the results of this study (Abdallah and Mayersohn, 1991; (Bowers, 1990]. Based on these results, the lecithin/**gelatin** formulation showed a 2.0-fold increase in bioavailability relative to the bulk powder.

DETD FIG. 5 illustrates the results of a study performed to determine the relative plasma concentration of cyclosporin over time following **oral** administration. The data illustrated in FIG. 6 suggests that coated cyclosporin powder was more readily dissolved into the intestinal lumen. . .

DETD As was stated above, the method of the present invention can include the manufacture of pharmaceutical ingredients treated with the lecithin/**gelatin** coating which is then lyophilized or the pharmaceutical ingredient treated with the lecithin/**gelatin** coating can be spray coated onto beads. Referring to FIG. 8, lyophilized cyclosporin formulation treated with the lecithin/**gelatin** coating and bulk cyclosporin powder were compared. The percentage cyclosporin dissolved in Milli-Q (Millipore, Corp.) (deionized, distilled water) over time is illustrated. The lyophilized cyclosporin coated with lecithin/**gelatin** demonstrated both a greater initial dissolution rate and greater overall percentage dissolution of coated cyclosporin as compared to the bulk. . .

DETD . . . order to ascertain in vitro data regarding the performance of the subject invention. Cyclosporin, a immunosuppressive drug, has an aqueous **solubility** of about 0.006 mg/ml. This compound was formulated with lecithin and **gelatin**, as described above, and its dissolution into 0.25% sodium lauryl sulfate was measured as shown in FIG. 2. The lecithin/**gelatin** formulation and the bulk powder form were treated in Simulated Intestinal Fluid, USP for two hours with 0.25% w/v sodium. . .

DETD As shown in FIGS. 3 and 8, in the simulated intestinal fluid, the amount dissolved of the lecithin/**gelatin** coated formulation was much greater than bulk powder which was essentially insoluble over the cause of the experiment.

DETD . . . performance of the subject invention. Cyclosporin was administered to dogs both as the bulk powder and formulated with lecithin and **gelatin** as described above. The lecithin/**gelatin** formula was prepared by dissolving one gm each of **gelatin**, USP/NF and lecithin NF in 100 ml of water. 0.5 gm of cyclosporin was added to this liquid and mixed. . . to coat the particles. The suspension was then placed on a freeze-drier and the moisture was removed by lyophylization. The lecithin/**gelatin** formulation and bulk powder were suspended in 10 ml of water administered via a gastric tube followed by 40 ml. . . content. FIG. 5 shows the results of this study [Abdallah et al., 1991; Bowers, 1990]. Based on these results, the lecithin/**gelatin** formulation showed a 2.0-fold increase in bioavailability relative to the bulk powder.

DETD The results of the above studies demonstrate that the lecithin/**gelatin** coating of the present invention greatly increases both the initial dissolution rate and total percentage dissolution of previously poorly water-**soluble** pharmaceutical ingredients. That is, the method of coating a poorly water-**soluble** pharmaceutical ingredient with a pharmaceutical excipient or coating formulation which includes lecithin and **gelatin** greatly increased both the initial dissolution rate and overall percent dissolution of the previously poorly water-**soluble** pharmaceutical ingredient. The increased dissolution of the pharmaceutical ingredients treated according to the present invention allows drugs which may have poor water-**solubility** to be utilized since the method and coating of the present invention greatly increases the dissolution rate of these poorly water-**soluble** pharmaceuticals contained therein.

DETD . . . been shown to function in vitro as well as in vivo. The present invention increases the dissolution rate of poorly water-**soluble** pharmaceutical ingredients without **solubilizing** and/or then recrystalizing the pharmaceutical ingredient thereby eliminating the necessity for recharacterization or reidentification the pharmaceutical

ingredient as discussed above. . .

DETD TABLE 1

Range of lecithin and **gelatin**
(% weight of final powder) = 1% to 40% (w/w).

Material	Range of Conc. in Coating Solution (% w/v)
lecithin	0.01-2.0
gelatin	0.01-2.0
drug	0.1-12

DETD TABLE 2

Relative Bioavailability in Dogs of Cyclosporin Given **Oral**
Comparing the Lecithin/**Gelatin** formulation with the Bulk Powder

Formulation	AUC-6 (μg-hr/ml)	Relative Increase in Bioavailabilty
cyclosporin bulk powder	0.7	1.0
lecithin/**gelatin** cyclosporin formulation	1.4	2.0

DETD TABLE 3

Examples of Currently Marketed Water Insoluble Drugs

Formulation	**Solubility** (mg/ml)	Dose (mg)	VISSOLUTION (liters)
Cyclosporin1	0.006	750	125
Griseofulvin2	0.017	500	29.4
Digoxin3	0.024	0.50	0.021
Nifedipine4	0.010	30.0	3.0
Itraconozole5	0.001	200	9.9
Carbamazepine6			

. . . Steimer, and W. Niederberger, J. Pharmacokinet, Biophar., 16:331-353 (1988).

2 Katchen, B. Symchowicz, S., J. Pharm. Sci., 56:1108 (1967). note: **solubility** was measured at 39° C.

3 J. B. Dressman, D. Fleisher, Mixingtank Model for Predicting Dissolution Rate Control of **Oral** Absorption, J. Pharm. Sci., 75:109-116 (1986).

4 D. R. Swanson, et al, Nifedipine Gastrointestional Therupeutic System, Amer J of Med,. . .

CLM What is claimed is:

. . . A method of making a pharmaceutical composition by coating at least one pharmaceutical ingredient with a mixture consisting essentially of **gelatin**, lecithin, and a solvent and drying the coated pharmaceutical ingredient to remove the solvent thereby increasing the dissolution rate of. . .

. . . 1, wherein said coating step is further defined as the steps of mixing said at least one pharmaceutical ingredient with **gelatin**, lecithin, and the solvent.

5. A method as set forth in claim 1 further including the step of dissolving the **gelatin** in an aqueous solvent prior to said coating step.

. . . method as set forth in claim 1 further including the step of coating beads with the pharmaceutical ingredient coated with **gelatin** and lecithin.

L16 ANSWER 8 OF 11 USPATFULL
Full-text
ACCESSION NUMBER: 97:91198 USPATFULL
TITLE: Method for making a multi-stage drug delivery system
INVENTOR(S): **Amidon, Gordon L.**, Ann Arbor, MI, United States

Crison, John R., Ann Arbor, MI, United States
PATENT ASSIGNEE(S): Port Systems, L.L.C., Ann Arbor, MI, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5674530		19971007
APPLICATION INFO.:	US 1995-383830		19950206 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1994-251731, filed on 31 May 1994, now patented, Pat. No. US 5387421 which is a continuation of Ser. No. US 1992-826253, filed on 27 Jan 1992, now abandoned which is a continuation of Ser. No. US 1991-648968, filed on 31 Jan 1991, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Bawa, Raj
LEGAL REPRESENTATIVE: Kohn & Associates
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 16 Drawing Figure(s); 7 Drawing Page(s)
LINE COUNT: 702
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of making a drug delivery system (10) includes the steps of filling a first water permeable capsule half with a drug and an osmotic agent and plugging an open-end (24) of the capsule (12). The method further includes the steps of disposing a water permeable film (30) over the capsule (12) and plug (28), filling a second capsule half (14) with a drug (18), and releasably mounting an open end (34) of the second capsule half (14) over the plugged end (24) of the first capsule half (12).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IN **Amidon, Gordon L.**, Ann Arbor, MI, United States
SUMM It has been recognized that there is a need for a drug delivery system which yields an increase in the **oral** dosing interval of drugs exhibiting presystemic loss metabolism while simultaneously maintaining bioavailability equivalent to the immediate release dosage form. Such drugs would otherwise either require short interval dosing, such as periodic **oral** dosing having short periods between each **oral** dosing.
SUMM . . . for emitting external fluid into the osmotic device. The device includes an opening having an erodible element, such as a **gelatin** plug that erodes and forms an osmotic passageway in the environment of use. Within the device is a modulating agent in nonequilibrium proportions. Upon the influx of fluid into the device, there is co-**solubilization** of a useful agent which is then released from the device. Thusly, co-**solubilization** of a modulating agent and a useful agent controls the release of the useful agent and results in the delayed. . .
SUMM . . . of drug will escape metabolism and therefore be available. For those drugs with incomplete absorption due to low permeability, poor **solubility** or in which case the absorption rate limited by rate of dissolution, enhancers can be added to increase the bioavailability.. . .
DETD The capsule halves 12,14 can be made from various materials, preferably water containing **gelatins**.
DETD A number zero hard **gelatin** two piece capsule was filled with 350 mg±1.5 mg of the fill mix or adjusted to give a potency of. . .
DETD . . . mg±1 mg of the captopril immediate release blend (50%) was disposed into the cap of the size number zero hard **gelatin** and mounted onto the capsule previously referred to above. The cap was placed on the body taking care not to. . .
DETD . . . coating or immersion coating of the capsules 12 include acetone for water insoluble materials and water (H O) for water **soluble** coating materials. Other suitable solvents known to those skilled in the art can also be used.
DETD A number zero hard **gelatin** two piece capsule (Capsugel, Greenwood, S.C.) was filled with 200 mg of the osmotic charge (sorbitol/lactose)-aspirin formulation. Gelucire 50/02 was. . .
DETD Capsules, prepared as described above numbered from 3 to 7, were used for bioavailability study. Captopril tablets and powder for **oral** and intravenous studies were kindly donated by Squibb. Two male beagle dogs, weighing thirty-four and thirty pounds and two midgut-fistulated. . .
DETD **Oral** study--Four tablets containing 25 mg of Captopril were given to four dogs orally with 20 ml of tap water. Dogs. . .
DETD The study was duplicated in each dog. The experimental design was the

same as the **oral** study except that the schedule for sample collection was every one hour for twelve to thirteen hours. Dogs were released. . .

DETD . . . time zero to infinity by extrapolating the last blood concentration with an elimination rate constant (ke) were evaluated from the **oral**, intravenous, and technology studies based on the noncompartmental analysis. Relative bioavailability of technology capsules were determined comparing to the **oral** study and normalized by the dose given.

DETD . . . USP 100.00
Lactose, Anhydrous, USP 41.00
Microcrystalline Cellulose, NF 97.35
Sorbitol, NF 35.00
Croscarmellose Sodium, NF 7.00
Magnesium Stearate, BP 1.75
Gelocire 50/02 120.00
Size #0 hard **gelatin** two piece capsules Captopril immediate release blend (50%) 66.00
Coating solution for captopril pulsatile release capsules q.s. to obtain suitable release

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*Microcrystalline. . .

L16 ANSWER 9 OF 11 USPATFULL
Full-text

ACCESSION NUMBER: 95:11441 USPATFULL
TITLE: Multi stage drug delivery system
INVENTOR(S): **Amidon, Gordon L.**, Ann Arbor, MI, United States
Leesman, Glen D., Ann Arbor, MI, United States
Sherman, Lizbeth B., Ann Arbor, MI, United States
PATENT ASSIGNEE(S): TSRL, Inc., Ann Arbor, MI, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5387421		19950207
APPLICATION INFO.:	US 1994-251731		19940531 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1992-826253, filed on 27 Jan 1992, now abandoned which is a continuation of Ser. No. US 1991-648968, filed on 31 Jan 1991, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Kishore, G. S.
ASSISTANT EXAMINER: Bawa, Raj
LEGAL REPRESENTATIVE: Reising, Ethington, Barnard, Perry & Milton
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 11 Drawing Figure(s); 6 Drawing Page(s)
LINE COUNT: 694
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A drug delivery system includes a first capsule half having an inner chamber for containing a drug therein. A plug is disposed in a passageway of the capsule half for plugging the opening thereof. The plug is releasable from the passageway opening upon the application of pressure from within the inner chamber. A pump mechanism causes an increase in pressure within the inner chamber and forces the plug out of the passageway to release the drug from the inner chamber and out of the passageway thereby providing a second pulse of drug release at a predetermined time after initial ingestion of the capsule. The invention further provides a method of manufacturing the drug delivery system and method by which the drug delivery system provides the drug to the body.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IN **Amidon, Gordon L.**, Ann Arbor, MI, United States
SUMM It has been recognized that there is a need for a drug delivery system which yields an increase in the **oral** dosing interval of drugs exhibiting presystemic loss metabolism while simultaneously maintaining bioavailability equivalent to the immediate release dosage form. Such drugs would otherwise either require short interval dosing, such as periodic **oral** dosing having short periods between each **oral** dosing.
SUMM . . . for emitting external fluid into the osmotic device. The device includes an opening having an erodible element, such as a **gelatin** plug that erodes and forms an osmotic passageway in the environment of use. Within the device is a modulating agent in nonequilibrium proportions.

Upon the influx of fluid into the device, there is co-**solublization** of a useful agent which is then released from the device. Thusly, co-**solublization** of a modulating agent and a useful agent controls the release of the useful agent and results in the delayed. . .

SUMM . . . of drug will escape metabolism and therefore be available. For those drugs with incomplete absorption due to low permeability, poor **solubility** or in which case the absorption rate limited by rate of dissolution, enhancers can be added to increase the bioavailability.. . .

DETD The capsule halves 12,14 can be made from various materials, preferably water containing **gelatins**.

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DETD . . . time zero to infinitive by extrapolating the last blood concentration with an elimination rate constant (ke) were evaluated from the **oral**, intravenous, and technology studies based on the noncompartmental analysis. Relative bioavailability of technology capsules were determined comparing to the **oral** study and normalized by the dose given.

DETD . . . USP 100.00

Lactose, Anhydrous, USP 41.00

Microcrystalline Cellulose, NF 97.35

Sorbitol, NF 35.00

Croscarmellose Sodium, NF 7.00

Magnesium Stearate, BP 1.75

Gelocire 50/02 120.00

Size #0 hard **gelatin** two piece capsules 66.00

Captopril immediate release blend (50%)

Coating solution for captopril pulsatile release capsules q.s. to obtain suitable release

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*Microcrystalline cellulose. . .

L16 ANSWER 10 OF 11 USPATFULL

Full-text

ACCESSION NUMBER: 93:58904 USPATFULL

TITLE: Pulsatile drug delivery system

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PATENT INFORMATION:	US 5229131		19930720
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LEGAL REPRESENTATIVE: Rohm & Monsanto

NUMBER OF CLAIMS: 18

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 11 Drawing Figure(s); 5 Drawing Page(s)

LINE COUNT: 1359

AB A drug delivery system for administering a drug in controlled pulse doses to an aqueous environment in the body of a living being has one or more, and preferably less than ten, individual drug-containing subunits in a unitary drug depot, such as a tablet or capsule. The individual

subunits are designed to dissolve at different sites and/or times in the gastrointestinal tract to release pulse doses of drug into the portal system in an analogous manner to the rate of release from an immediate release dosage form administered according to an appropriate dosing schedule. The dissolution time of the individual subunits can be controlled by several methods including the provision of pH-sensitive enteric coatings and permeability-controlled coatings. The drug delivery system has significant advantages for the **oral** administration of first-pass metabolized drugs which exhibit a non-linear relationship between input rate of the drug into the portal system and bioavailability.

IN **Amidon, Gordon L.**, Ann Arbor, MI, United States

AB . . . methods including the provision of pH-sensitive enteric coatings and permeability-controlled coatings. The drug delivery system has significant advantages for the **oral** administration of first-pass metabolized drugs which exhibit a non-linear relationship between input rate of the drug into the portal system. . .

SUMM There is therefore a need for a drug delivery system which yields a reduction in the **oral** dosing interval of drugs exhibiting first-pass metabolism while simultaneously maintaining bioavailability equivalent to the immediate release dosage form.

SUMM . . . drug phenytoin. Given the large number of drugs which are eliminated by metabolism, there is a great need for an **oral** dosage form which reduces the relative extent of metabolism.

SUMM . . . dosing schedules and permit allowance for circadian rhythms to optimize plasma level time profiles throughout the day and night; and **oral** delivery of drugs which undergo particularly extensive first-pass metabolism (both gastro-intestinal and hepatic).

SUMM . . . system of this type. In fact, at the present time, the operating principles of available controlled release dosage forms for **oral** delivery are based on relatively simple transport models which do not take into account many of the critical factors required. . .

SUMM It is another object of this invention to provide a drug delivery system which reduces **oral** dosing intervals for first-pass metabolized drugs, and hence improves patient compliance, while maintaining bioavailability equivalent to the immediate release dosage. . .

SUMM It is yet a further object of this invention to provide a drug delivery system which permits efficacious **oral** delivery of nonlinear first-pass drugs of the type which are extensively metabolized both gastro-intestinally and hepatically.

SUMM . . . is also a further object of this invention to provide a drug delivery system which yields a reduction in the **oral** dosing interval of drugs exhibiting first-pass metabolism while simultaneously maintaining bioavailability equivalent to the immediate release dosage form.

SUMM A still further object of this invention is to provide a drug delivery system for **oral** administration of a drug which reduces the relative extent of metabolism of the administered drug.

SUMM . . . coating portion which is provided with first and second polymer materials which are each pH-responsive. The pH-responsive polymer materials are **soluble** in the aqueous environment in response to the pH characteristic of the environment over a predetermined pH-responsive period of **solubility** to release drug to the environment. In such an embodiment, the pH-responsive material is selected from the group consisting of. . .

DRWD FIG. 2 is a graphical depiction of plasma level time curves for the **oral** administration of propranolol in a drug delivery system of the present invention for two dogs;

DETD This drug delivery system has significant advantages for the **oral** administration of first-pass metabolized drugs which exhibit a non-linear relationship between input rate of the drug into the portal system. . .

DETD . . . the individual unit cores. The individual units are combined into a unitary depot which may be single tablet or a **gelatin** capsule or any other form known in the art.

DETD . . . 8-16 hour release form. The subunits may be combined into a single unitary body, such as a tablet or hard **gelatin** capsule, in any manner known in the art. Of course, these examples are only illustrative of the many specific embodiments. . .

DETD Characteristics of suitable enteric coatings include: insolubility in the stomach, **solubility** in the intestines, no toxicity, moisture permeability resistance, stability, and good coating capability. A widely used enteric coating, and one. . .

DETD . . . latexes, ethyl cellulose and cellulose butyrate and Eudragit RS

and Eudragit E 30 D. Although some of these polymers are **soluble** in organic solvents and applied in a weight percentage of organic solvent, such as acetone, others are water-based. Plasticizers include. . .

DETD

NaCl	100.0 mg
Avicel pH 102	100.0 mg
NaCMC (High Viscosity)	25.0 mg
AcDiSol	20.0 mg
Phenol Red	0.5 mg
Propranolol HCl	2.0 mg
Oil **Soluble** Dye	0.25 mg
Lactose qs	500.0 mg

DETD . . . osmotic pressure in the core will remain constant until the concentration of the osmotic agent in the core falls below **solubility** at which time, π will decrease due to dilution.

DETD . . . to 7. The IV results are shown as a " ." Similarly, blood plasma samples were withdrawn and analyzed for **oral** administration of 80 mg propranolol in immediate release form (" ") and the polymer coated dosage delivery form of section. . .

DETD . . . dosing, propranolol undergoes an initial distribution phase followed by a terminal phase with a half-life of about. 120 minutes. After **oral** (PO) dosing with the immediate release dosage form (INDERAL-80 mg), the tablet rapidly dissolved and the blood levels of free. . .

DETD The average AUC and standard error for the two **oral** dosage forms are comparable and are shown below:

CLM What is claimed is:

. . . 1 wherein the aqueous environment has predetermined pH characteristics, said first and second polymer materials are pH-responsive materials, each being **soluble** in an aqueous environment having a respective predetermined pH, whereby said respective coating portion dissolves after expiration of the respective. . .

L16 ANSWER 11 OF 11 USPATFULL

Full-text

ACCESSION NUMBER: 87:56611 USPATFULL

TITLE: Lipid osmotic pump

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PATENT INFORMATION:	US 4685918		19870811	
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PRIMARY EXAMINER: Kight, John

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NUMBER OF CLAIMS: 19

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 28 Drawing Figure(s); 25 Drawing Page(s)

LINE COUNT: 1250

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The instant invention is directed to a lipid osmotic pump, comprising:

(A) a core, comprising:

(i) a beneficial amount of at least one substantially water insoluble active agent which is lipid **soluble** and/or lipid wettable;

(ii) a sufficient amount of at least one water immiscible lipid carrier, which is liquid at the temperature of intended use, to dissolve and/or suspend said active agent; and

(iii) a sufficient amount of at least one osmotic agent to ensure release of said lipid carrier from the pump; and

(B) surrounded by a water insoluble wall:

(i) having a thickness of about 1 to 1000 microns;

(ii) which is preferentially wetted by said lipid carrier over an aqueous solution of said osmotic agent;

(iii) having a water permeability of about 1×1018 to 4×1015 cm sec/g;

(iv) prepared from at least one polymer permeable to water but substantially impermeable to said osmotic agent; and

(v) having a means for said active agent and lipid carrier to be released through said water insoluble wall.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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AB (i) a beneficial amount of at least one substantially water insoluble active agent which is lipid **soluble** and/or lipid wettable;

SUMM The present invention concerns an osmotically activated system for dispensing beneficial, preferably pharmacologically, active agents which have poor **solubility** in water. The system comprises an inner core compartment of active agent(s), lipid carrier(s) and osmotic agent(s) preferably in admixture,. . .

SUMM . . . and sizes of tablets, pellets, multiparticulates, and such related dosage forms as familiar to those skilled in the art of **oral**, buccal, vaginal, rectal, nasal, ocular, aural, parenteral and related routes of administration.

SUMM . . . of the active agent(s) to be incorporated into the lipid, other than that it be substantially water insoluble and lipid **soluble** and/or lipid wettable. Likewise the key to the invention is not in the selection of the osmotic agent. The keys. . .

DRWD FIG. 5 is a cutaway and cross-section of a hard **gelatin** capsule filled with lipid osmotic pump pellets.

DETD (i) a beneficial active amount of at least one substantially water insoluble active agent which is lipid **soluble** and/or lipid wettable;

DETD . . . about 10% of the drug partitions into the aqueous phase throughout the time of lipid release. By the phrase "lipid **soluble** and/or lipid wettable" is meant that the active agent remains associated with the lipid carrier rather than the solution of. . .

DETD . . . antidiarrheal, and antiulcer histamine-H -antagonists such as bethanechol, clidinium, dicycloine, meclizine, prochlorperizine, trimethobenzamide, loperamide, cimetadine, ranitidine, diphenoxylate, famotidine, and omeprazole; **oral** hypoglycemics such as chlorpropamide, tolazamide, and tolbutamide; anticoagulants such as warfarin, phenindione, and anisindione; anti-infective agents including antibiotic, antimicrobial, antiviral,. . .

DETD . . . be suitable for use herein such as esters of acids or alcohols and amides. Also a drug that is water **soluble** can be chemically modified to make it less water **soluble** and more lipid **soluble**. Such drugs or complexes can be delivered from the device and can be converted by enzymes, hydrolyzed by body fluids. . .

DETD . . . purified and specially selected palm-seed oil, such as coconut and palm-kernel oil. The amount of lipid carrier depends on the **solubility** of the agent in the carrier or the amount needed for a suspension of the drug. This can range from. . .

DETD . . . can be generated, however osmotic pressures greater than zero are within guidelines. The amount of osmotic agent depends on its **solubility** in water and the total volume of the core. A sufficient amount of osmotic agent is required to ensure complete. . . necessary to maintain a saturated solution of osmotic agent throughout the period of lipid pumping. Thus the ratio of the **solubility** to the density (s/p) is an indication of the efficiency of the osmotic agent. A lower s/p ratio indicates a. . . tartaric acid, carbohydrates such as fructose, sucrose, glucose, α-d-lactose monohydrate, and mixtures thereof. The osmotic agent(s) may be a water **soluble** active agent(s); however, a water insoluble active agent is still required. The compound is initially present in excess and it. . .

DETD . . . osmotic agent, preferably
better than cellulose
acetate CA-320S

3. Water permeability
1 × 1018 to 4 × 1015
cm sec/g

4. Water **Soluble** Pore-
0 to 150 parts,
forming additives

preferably 5 to 100
parts, per 100
parts wall polymer(s)

5. Plasticizer and flux

. . .

DETD . . . the like. The saccharides include the sugars, sucrose, glucose, fructose, mannose, galactose, aldohexose, altrose, talose, lactose, monosaccharides, disaccharides, and water **soluble** polysaccharides. Also, sorbitol, mannitol, organic aliphatic and aromatic polyols, including diols and polyols, as exemplified by polyhydric alcohols, poly(alkylene glycols), polyglycols, alkylene glycols, poly(α-ω)alkylenediols esters or alkylene glycols, poly vinylalcohol, poly vinyl pyrrolidone, and water **soluble** polymeric materials may be used. Pores may also be formed in the wall by the volatilization of components in a. . .

DETD . . . by cold or hot stretching at low or high temperatures until pores are formed, by leaching from a polymer a **soluble** component by an appropriate solvent, by ion exchange reaction, and by polyelectrolyte processes. Processes for preparing microporous materials are described. . .

DETD . . . Also, a detailed description pertaining to the measurement of plasticizer properties including solvent parameters and compatibility such as the Hildebrand **solubility** parameter, δ, the Flory-Huggins interaction parameter, χ, and the cohesive-energy density, CED, parameters are disclosed in Plasticization and Plasticizer Processes,. . .

DETD . . . of the wall creating pores from which the contents can be pumped. Also shown in FIG. 5 is a hard **gelatin** capsule (31) filled with the pellets (30) which illustrates one method of administering this type of dosage form.

DETD . . . chloride (osmotic agent) and 2 g of timolol anhydrous free base (active agent) and 0.14 g of scarlet red (lipid **soluble** dye) were melted together. Upon melting, the timolol and scarlet red dye dissolved in the lipid carrier and the sodium. . .

DETD . . . and be retained on a 170 mesh screen 150 g Witepsol® H-35 (lipid carrier) and 0.35 g scarlet red (lipid **soluble** dye) were added to a 250 ml stainless steel beaker and heated to 45° C. by means of a heating. . .

DETD . . . g cellulose triacetate (Eastman CA-436-80S), 12.5 g polyethylene glycol 400 (plasticizer and flux enhancing agent), 50 g tartaric acid (water **soluble** pore-former), 750 ml dichloromethane, and 250 ml methanol. The coating solution was applied for a period of 20 minutes at. . .

DETD . . . the beads to the flasks, 50 ml of IPM was added to each flask to aid in analysis of the lipid-**soluble** dye or active agent to be release from the beads. These samples of coated beads are typical of the amounts commonly filled in hard **gelatin** capsules for **oral** administration. FIG. 5 depicts a hard **gelatin** capsule, (31) filled with microporous-coated beads, (30). Each bead is comprised of a microporous coating, (29) and a core containing. . .

CLM What is claimed is:

. . . comprising an admixture of: (i) a beneficial amount of at least one substantially water insoluble active agent which is lipid **soluble** and/or lipid wettable; (ii) a sufficient amount of at least one water immiscible lipid carrier, which is liquid at the. . . said water insoluble wall; (C) wherein at the temperature of use, the lipid carrier is liquid and retains the lipid **soluble** or lipid wettable agent in a dissolved or suspended state so that upon the dissolution of the osmotic agent in. . .

16. The lipid osmotic pump of claim 1, wherein said osmotic agent is a water **soluble** active agent.

17. A water **soluble** capsule containing at least two osmotic pumps of claim 1.

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